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The Dawn of a New Digital Age: Addressing the Impact of ChatGPT and Artificial Intelligence in the Field of Medicine

Dr Geoffrey Everest Hinton is a leading figure in the deep learning community and is regarded as one of the three Godfathers of Artificial Intelligence (AI). In May this year, Dr Hinton publicly announced his departure from Google because he wanted to freely speak about the risks of AI. In this light, we as medical professionals must also be aware of the potential existential risks arising from its deliberate misuse by malicious people.

Artificial Intelligence assumes that thinking and reasoning can be replicated and mechanized. It has become the "flavor of the day" or the next big thing, and its use is advancing rapidly. It is no longer science fiction; AI has emerged as a powerful reality in today's world. We now live in the digital age of 'Big Data' and its applications are now increasingly finding a place in most industries, including medicine. We are already using Big Data daily. It is already integrated into our everyday lives through tools such as Google Maps, facial recognition, and digital smart assistants such as Apple's Siri, Google Home, and Amazon's Alexa while more and more applications are being developed and introduced every day.

Artificial Intelligence: Chat Generative Pre-Trained Transformer (ChatGPT)

The recent introduction of Chat Generative Pre-Trained Transformer (ChatGPT), the latest large language model (LLM), prompted many to reflect on the exciting ways AI can impact our lives in the very near future. With ChatGPT, you can ask a question and receive a properly punctuated grammatically correct answer within seconds. Chat Generative Pre-Trained Transformer gained over 100 million users within two months of its launch, establishing itself as the fastest-growing consumer application in history [1].

Like all other LLM-based AIs, ChatGPT uses extensive text datasets to generate new text matching the text it was trained on, requiring understanding, interpreting, and generating human language via computer systems [2]. GPT-4, the latest version of ChatGPT, does not directly have internet access and has only been trained on information available up until 2021. On the other hand, while Google's Bard AI language model (currently available only via waitlist) allows access to Google's search engines, it is not readily available to everyone. Therefore, ChatGPT is the most powerful language model presently available.

Chat Generative Pre-Trained Transformer (ChatGPT) in Medicine and Clinical Research

Chat Generative Pre-Trained Transformer is currently one of the largest and most powerful AI processing models today. It has 175 billion language parameters and is used in a variety of industries like technology, banking, marketing, and entertainment. It will quickly broaden its use into medicine and clinical research.

Recent scientific literature has examined ChatGPT's impact on the field of medicine. While some studies have shown that it is helpful for conversational and writing tasks, increasing efficiency and accuracy of output, others have identified its limitations in medical research [3].

Factual Inaccuracies of Large Language models (LLMs)

The major and most consequential downside of ChatGPT, and other future LLMs, is the potential risk of presenting incorrect data in a medical or scientific setting. Furthermore, its information may also turn out to be not accurate, making it an imperfect tool for medical research. One needs to remember that presenting incorrect information can carry significant and harmful risks.

This risk was highlighted in a Northwestern University study [4]. Researchers used ChatGPT to write 50 medical-research abstracts based on articles published in medical journals. When given a mixture of original and general abstracts, blinded human reviewers correctly identified 68% of generated abstracts as being generated by ChatGPT, but they also incorrectly identified 14% of original abstracts as being generated. The reviewers indicated that it was surprisingly difficult to differentiate between the two.

The results of this study are encouraging some researchers to use ChatGPT as a writing tool, since people reading their papers may not recognize that their words were actually generated by AI. The study highlights the potentially dangerous risk that ChatGPT is able to mislead human reviewers in a medical setting. False research may lead to inappropriate medical decisions based on imprecise information, which in turn could have detrimental results for our patients.

Can Chat Generative Pre-Trained Transformer (ChatGPT) Still Be Useful in Medical Research?

Currently, ChatGPT has data only from 2021 and earlier. For this reason, there are instances of factual inaccuracies from outdated information. However, by recognizing the potential problems with ChatGPT, the scientific community can harness its helpfulness. An article published in Nature in February 2023 described computational biologists using ChatGPT to improve finished research papers and received outputs with increased readability and better-edited manuscripts [5].

Using ChatGPT for the purpose of delegating tedious tasks like proofreading and editing, increases productivity and content quality would allow researchers to devote more time in advancing their field of medicine.

There will be continuous advancements and constant evolution of LLMs. It is therefore important to understand the capabilities and limitations of AI. In view of the potential risks arising out of AI possibly using inaccurate or outdated information, at the moment, it is not advisable to rely on ChatGPT as the sole source of references or facts. While it cannot replace human expertise, ChatGPT can nowadays already make tedious tasks such as editing a lot easier.

Can Artificial Intelligence (AI) Completely Replace Medical Practitioners?

At present, several different AI systems are being used by payers and providers of healthcare and life sciences companies. Advancements in AI, such as ChatGPT, will serve as an usher in more advanced AI systems. It has the potential to improve the delivery of healthcare and make it more efficient by improving diagnostics, analysis of large datasets, and reducing the burden of administrative paperwork. However, AI will never be able to replace medical practitioners.

With advancements in AI and other technologies, fully autonomous robotic systems will be the next reality. However, the job of a medical practitioner goes far beyond seeing patients and providing treatment [6]. The medical practitioner's role is centered around providing personalized treatment along with the human to human touch. Despite the advances in AI, medical tasks will still require the application of specialized subject knowledge and opinions, coupled with genuine human compassion.

Therefore, the potential of using AI in healthcare primarily lies in its ability to increase efficiency by redistributing workload, optimizing performance, and improving patient care through a collaborative synergy between man and machine. Artificial Intelligence cannot and should not replace medical practitioners.

Human Intelligence (HI) - Artificial Intelligence (AI): A collaboration between Man and Machine

Human intelligence (HI) differs from AI in its biological evolutionary history, adaptability, creativity, emotional intelligence, and ability to comprehend complex abstract concepts [7]. Artificial Intelligence cannot replace human professionals in the field of medicine and clinical research. Therefore, AI and HI should collaborate to capitalize on their respective strengths.

Artificial Intelligence in the context of LLM applications, can only create knowledge with the help of historic inputs from established research that has been previously conducted and already available. It cannot create new knowledge like humans can. Without human beings, medical and scientific progress is not possible. Well-trained and highly qualified human researchers are necessary to discover new knowledge and scientific breakthroughs. LLMs are only effective as a complement to medical research. Moreover, AI cannot be used as definitive data or evidence without considering its limitations, risks, and factual inaccuracies as discussed earlier.

Let's keep in mind that the algorithms of ChatGPT and other LLMs are only as good as the old data on which they are trained. Continued training will further improve them, and this will serve to facilitate progress in the medical field. The use of collaborative intelligence, where humans and AI work together, is essential to ensure that we fully leverage the strengths of both to achieve the best possible outcomes [8].

Conclusion

With the advancement of technology over time, AI can be harnessed to be used in increasingly sophisticated ways to facilitate and advance the field of medicine. Chat Generative Pre-Trained Transformer used as a tool for medical purposes is already being tested and will continue to be evaluated regardless of whether it has been trained specifically on medical data [9]. Discussions about its benefits, potential hazards, possible areas of applications, or needed regulations are also ongoing [10].

We are at the infancy of the use of AI in medicine and there is no limit to how far AI can bring us in the future. We live in an exciting and inspiring time for medicine. It is imperative, however, that regulations and frameworks are in place to guide its application. Medical practitioners must guide the use of AI correctly, so that AI's potential is only utilized appropriately to facilitate the progress of medicine.

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Kenneth Thean, MD

Editor

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Overview of Regenerative Medicine in Malaysia

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Abstract

Regenerative medicine is a fast-evolving discipline that has the potential to revolutionize healthcare through replacements or reparations of damaged tissues and organs. Stem cell therapy and tissue engineering have been the focus of regenerative medicine research and development in Malaysia. However, several challenges related to this field of medicine need to be addressed. Therefore, several different measures had been taken by the Malaysian government includes establishment of the National Committee on Stem Cell Research and Therapy and the issuance of guidelines for the use of stem cells in clinical practice to ensure a better development of the regenerative medicine filed in Malaysia.

Keywords: Regenerative medicine, Stem cell therapy, tissue engineering

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Regenerative medicine is a rapidly developing field that has the potential to revolutionize healthcare by replacing or repairing damaged tissues and organs. The field of regenerative medicine includes stem cell therapy, tissue engineering, gene therapy, and other innovative approaches that utilize the body's own mechanisms for healing and regeneration.

Regenerative medicine has the potential to revolutionize the way we treat a wide range of medical conditions, including cancer, diabetes, heart disease, and neurodegenerative disorders. In a nutshell, regenerative medicine application can be divided into:

1. Tissue engineering: Tissue engineering involves the use of biomaterials and stem cells to improve, repair and create functional tissues and organs in the laboratory. This approach has been used successfully to create skin, cartilage, and even organs such as the heart and liver from various natural and synthetic biomaterials [1]. However, previous studies addressed the issue of having limited clinical application in the tissue engineering field due to lack of collaboration between medical doctors and biomaterials scientists [1, 2].
2. Gene therapy: Gene therapy involves the use of genetic engineering techniques to modify a patient's DNA to treat or prevent a disease such as clustered regularly interspaced short palindromic repeat-associated protein 9 (CRISPR-Cas9) genome editing tool. This approach has been used successfully to treat certain genetic disorders, such as Parkinson's disease, Huntington's disease and Duchenne muscular dystrophy [3]. However, most of the gene therapies application are limited to in vivo and in vitro studies due to ethical consideration in human genetic manipulation [4].
3. Stem cell therapy: Stem cell therapy involves the transplantation of stem cells into a patient to replace damaged or diseased cells. This approach has been used successfully to treat various conditions associated to neurodegenerative disease and macular degeneration. Nevertheless, previous study by Aly[5] highlighted the need to prepare regulatory guideline since there was an increasing number of clinics in providing unproven stem cell- based treatments which could jeopardize patient safety.

In Malaysia, regenerative medicine research and development are gaining momentum, with a focus on stem cell therapy and tissue engineering. This article provides an overview of the regenerative medicine landscape in Malaysia, including the current research, challenges, and government initiatives.

Stem Cell Therapy in Malaysia

Stem cells are undifferentiated cells that have the potential to differentiate into various cell types and have the ability to regenerate damaged tissues. In Malaysia, stem cell research has been ongoing since the early 2000s, with the establishment of the National Stem Cell Centre which responsible for overseeing the ethical, legal, and regulatory aspects of stem cell research and therapy. Since then, several public and private institutions in Malaysia have been conducting stem cell research and providing stem cell therapy. Additionally, Malaysian Stem Cell Registry (MSCR) was also established as a platform for eligible people among public who want to donate their stem cell voluntarily to patients in need.

However, the effectiveness and safety of some of these therapies are still being investigated, and there is a lack of standardized protocols and regulations governing stem cell therapies. A study conducted by Tran et al[6] evaluated the regulation of stem cell therapy in Malaysia and found that there is a need for standardized guidelines and regulations to

ensure the safety and effectiveness of stem cell therapies. The researcher suggested that the Malaysian regulatory bodies involved in regenerative medicine and healthcare such as Ministry of Health (MOH) and National Pharmaceutical Regulatory Agency (NPRA) should establish a more comprehensive regulatory framework to oversee the use of stem cells in clinical practice.

Tissue Engineering in Malaysia

Tissue engineering is derived from biomedical engineering which involves the use of cells, scaffolds, and growth factors to create functional tissues or organs as shown in Figure 1[7]. In Malaysia, tissue engineering research is primarily focused on skin and bone tissue engineering. Researchers at Universiti Kebangsaan Malaysia (UKM) are developing a 3D- printed scaffold for bone tissue engineering [8]. The scaffold is made of biodegradable materials and can be implanted into the body to stimulate bone regeneration. Past study by Morshed et al[9] investigated the use of tissue engineering for skin regeneration in Malaysia and found a skin substitute using keratinocytes and fibroblasts, which can be used totreat burns and other skin injuries.

Challenges in Regenerative Medicine in Malaysia

Despite the progress made in regenerative medicine research and development in Malaysia, several challenges need to be addressed. One of the main challenges includes the lack of definite understanding on ethical guideline among ethics committee which involve conceptual framework, safety and efficacy in conducting research associated to regenerative medicine [4, 10, 11]. Subsequently, ethical issue in regenerative medicine may impede the application of research grant for the research study funding. Consequently, this will create a huge gap for researchers to design and conduct acceptable clinical trials on regenerative medicine besides time and cost-consuming procedures.

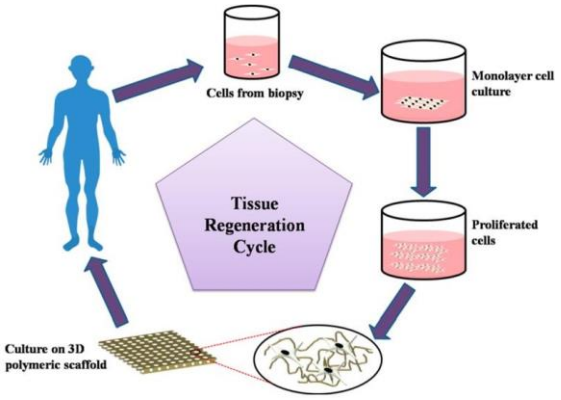

Figure 1: Basic principle procedure for tissue engineering [7]

Another challenge is the shortage of skilled personnel, particularly in the area of stem cell research and therapy. The demand for stem cell therapy is increasing, but there is a shortage of trained personnel to provide these therapies. This shortage is due to the limited fund, specialized equipment, lack of formal training programs and educational opportunities in regenerative medicine in Malaysia [12].

Regulatory Framework for Regenerative Medicine in Malaysia

The regulatory framework for regenerative medicine in Malaysia is still evolving, and there is a need for standardized guidelines and regulations to ensure the safety and effectiveness of regenerative medicine products. In 2009, MOH has issued guidelines for the regulation of stem cells in clinical practice. The guideline was prepared by Stem Cell Research and Ethics Subcommittee of National Stem Cell Committee in collaboration with Medical Development Division of the Ministry of Health to develop policies, requirements, framework and guidelines for stem cell research and therapy in Malaysia [13]. Nevertheless, Gopalan et al[14] revealed that the guideline is inefficient in providing good ethical governance of the technology and suggest to provide more comprehensive stem cell therapy guideline that align to Guideline for Stem Cell Research and Clinical Translation (ISSCR) for more relevant and advanced regenerative medicine application.

Additionally, National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health which was established in 1978 to help protect public's healthcare by ensuring approved therapeutic substances and meet the guideline before marketed locally. With the increasing awareness of the importance of regenerative medicine, NPRA has prepared Malaysian Guidance Document and Guideline for Cell and Gene Therapy Products (CGTPs) in 2016 which help to facilitate and provide guidance for regenerative medicine application [15]. However, Imran et al[12] argued that the guideline needs to be specific and focused since it was too brief.

Furthermore, the Malaysian Bioeconomy Development Corporation (Bioeconomy Corporation) has been established under the purview of Ministry of Science, Technology and Innovation (MOSTI) since 2005 to promote the development of biotechnology and life sciences in the country. Bioeconomy Corporation provides funding, resources, and support to biotech companies and research institutions in Malaysia, including those involved in regenerative medicine research.

Conclusion

In conclusion, regenerative medicine is a promising field that has the potential to transform healthcare by providing new and innovative treatments for a wide range of conditions. In Malaysia, regenerative medicine research and development are gaining momentum, with a focus on stem cell therapy and tissue engineering. However, there are still several challenges that need to be addressed, including the lack of funding and trained personnel, and the need for standardized guidelines and regulations for the use of regenerative medicine products. The government of Malaysia has taken steps to address these challenges, including the establishment of the National Committee on Stem Cell Research and Therapy and the issuance of guidelines for the use of stem cells in clinical practice.

Overall, the future of regenerative medicine in Malaysia looks promising, and further investment and research in this field have the potential to benefit not only Malaysians but also the global healthcare community.

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Clinical, Dermoscopy and Histopathological findings of Exogenous Ochronosis: A Case Series

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Abstract

Hydroquinone is the gold standard of treatment for disorders of hyperpigmentation. However, complications such as Exogenous Ochronosis has become widespread due to its prolonged use. Clinical differentiation from other disorders of hyperpigmentation is difficult hence, correlation of dermoscopy and histopathology is warranted. Findings of blue-gray amorphous structures and hypopigmented areas of atrophy (confetti-like areas of depigmentation) in dermoscopy correlated with crescentic or "banana shaped" ochre-colored pigments and solar elastosis consistent with the diagnosis of Exogenous Ochronosis. The use of dermoscopy as a non-invasive tool is essential in distinguishing Exogenous Ochronosis from other disorders of hyperpigmentation. This aids in planning therapeutic options and improve patient outcomes.

Keywords: Exogenous Ochronosis, Dermoscopy, Hydroquinone, Histopathology

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The Asian cosmetic market for whitening is growing rapidly and its demand increasing, due to aesthetic and cultural desires [1]. Its vast availability online and claims of great results have encouraged people to purchase and use these products without medical supervision [2] Therefore, many complications are now being observed due to its misuse.

Hydroquinone remains to be the gold standard for conditions of hyperpigmentation [3]. Its unregulated presence over the counter has made has made its complications more visible. One of its dreaded complications is Exogenous Ochronosis (EO). Exogenous Ochronosis has first been defined by Findlay et al[4] with its association with using topical hydroquinoine in 1975. It is a paradoxical hyperpigmentation that appears as gray-brown or blue-black macules and caviar-like papules on photo-exposed areas and osseous surfaces with contact to the chemical [5, 6]. It is cosmetically disfiguring and thus causes psychological turmoil among patients. Due to its clinical similarity to other pigmentary disorders, it may be difficult to differentiate one from the other. Hence, its correlation with dermoscopy and histopathology is warranted to clinch proper diagnosis and improve patient outcomes and expectations.

Case Report

Ten (10) cases of exogenous ochronosis were seen at the Research Institute for Tropical Medicine Manila, Philippines from March 2007- August 2019 with a male to female ratio of 1:9. Average age of patients was 53 years old. None of the patients presented with signs of endogenous ochronosis such as arthralgia, dark colored urine, hyperpigmentation of the sclerae, thickening of the pinnae nor dark cerumen.

All 10 patients used hydroquinone 2% solutions without sun protection for a mean duration of 5.3 years (Table 1). Clinically, the most common features observed were, confetti-like depigmentation (Figure 1a) in 80% of cases, caviar-like papules (Figure 1b) and visible telangiectasias (Figure 1c) in 40% of patients. All patients exhibited lesions on the malar area. Meanwhile 60% of patients showed lesions on the nasal area and 40% on the perioral area. Other patients showed lesions on the chin, upper eyelid, forehead, anterior chest and lateral eyebrows with decreasing frequency (Table 2).

Table 1: Demographic Data

Patient	Sex	Age in years	Duration of Hydroquinone2% use
1	F	59	2 years
2	F	48	1 year
3	F	52	1 year
4	F	50	nil
5	F	50	10 years
6	F	56	5 years
7	F	49	8 years
8	F	53	6 years
9	M	60	10 years
10	F	55	5 years

Table 2: Area of distribution

Area of Distribution	Frequency
Malar	100%
Nasal	60%
Perioral area	40%
Chin	30%
Upper eyelid	20%
Forehead	20%
Anterior Chest	10%
Lateral eyebrows	10%

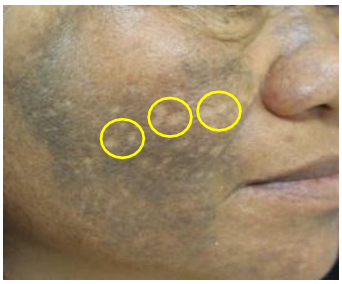

Figure 1a Confetti-like Depigmentation

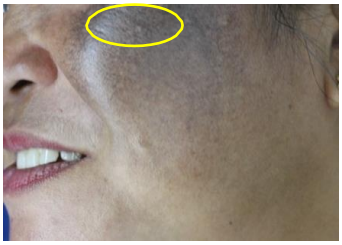

Figure 1b Caviar-like papules

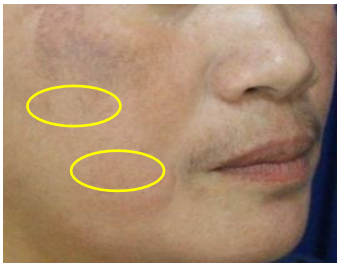

Figure 1c Visible Telangiectasias

Dermoscopy of all patients showed blue gray and black dots, annular and arcuate structures, reddish to dark -brown curvilinear structures, obliteration of follicular openings and telangiectasias. While only 80% of patients showed confetti-like depigmentation (Figure 2a and 2b). Histopathology findings showed the pathognomonic finding of ochre-colored bodies in various shapes and sizes seen in the papillary dermis (100%) (Figure 3a). Other nonspecific features included, acanthosis (20%) and epidermal atrophy (10%). Other findings in the dermis include solar elastosis (50%), perivascular infiltrate of lymphocytes (50%), and presence of telangiectasia (40%) (Figure 3b).

Discussion

The term Ochronosis was first described in 1866 by Virchow. This was used to describe ocher colored pigments located in connective tissues of various organs [7]. It was in 1975 when Findlay et al[4] first described this condition as an epidemic in Transvaal South Africa due to overuse of topical hydroquinone.

Its exact incidence globally remains unknown. However, the largest case series reported was in South Africa where 28-35% of the black population were affected by exogenous ochronosis due to hydroquinone containing products. However, its increasing incidence has also been seen in Asia [7, 8].

The exact pathogenesis of exogenous ochronosis remains unknown. However, a theory on its etiology was described by Penny's et al[9] and is still the most acceptable theory being used to date. It is hypothesized that hyperpigmentation is due hydroquinoine's competitive inhibition of homogentisic oxidase. This leads to formation and accumulation of homogentisic acid and other metabolic products that polymerizes to form ochronotic pigments deposited in the papillary dermis [7,10]. Another study done in 2019 at Boston University showed that tyrosinase inhibition of hydroquinone also plays a role on histopath findings in EO. This inhibition leads to decreased photoprotection leading to deeper penetration of UV radiation and solar elastosis [11]. These findings translate clinically as gray-brown, blue black macules or papulonodules (ochronotic pigments) on the background of chronically sun damaged skin (solar elastosis) on sun exposed areas and osseous surfaces [7].

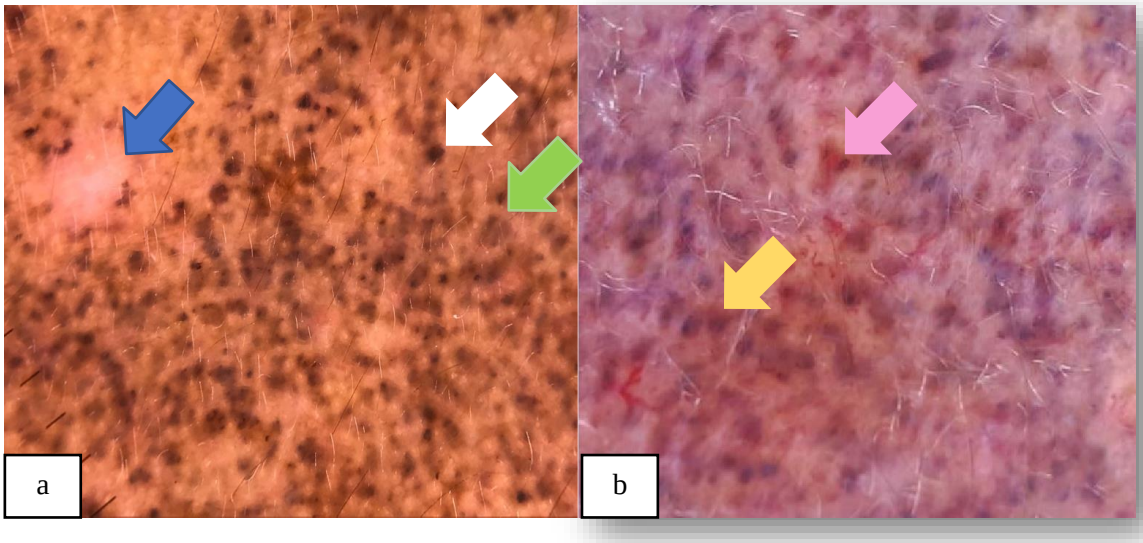

Figure 2a blue gray and black dots (white arrow); annular and arcuate structures (green arrows) confetti- like depigmentation (blue arrow).
Figure 2b reddish to dark brown curvilinear structures (yellow arrow); telangiectasia (pink arrow).

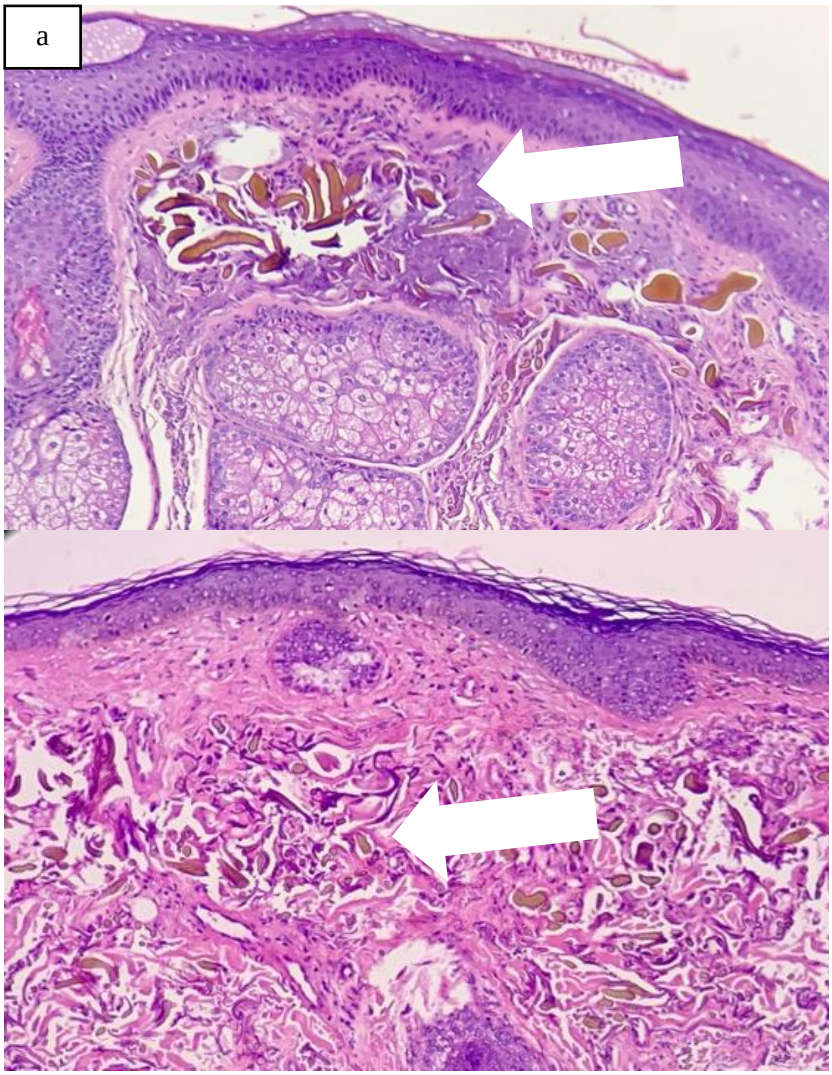

Figure 3a LPO view; Diagnostic finding of ochre colored bodies (white arrow)

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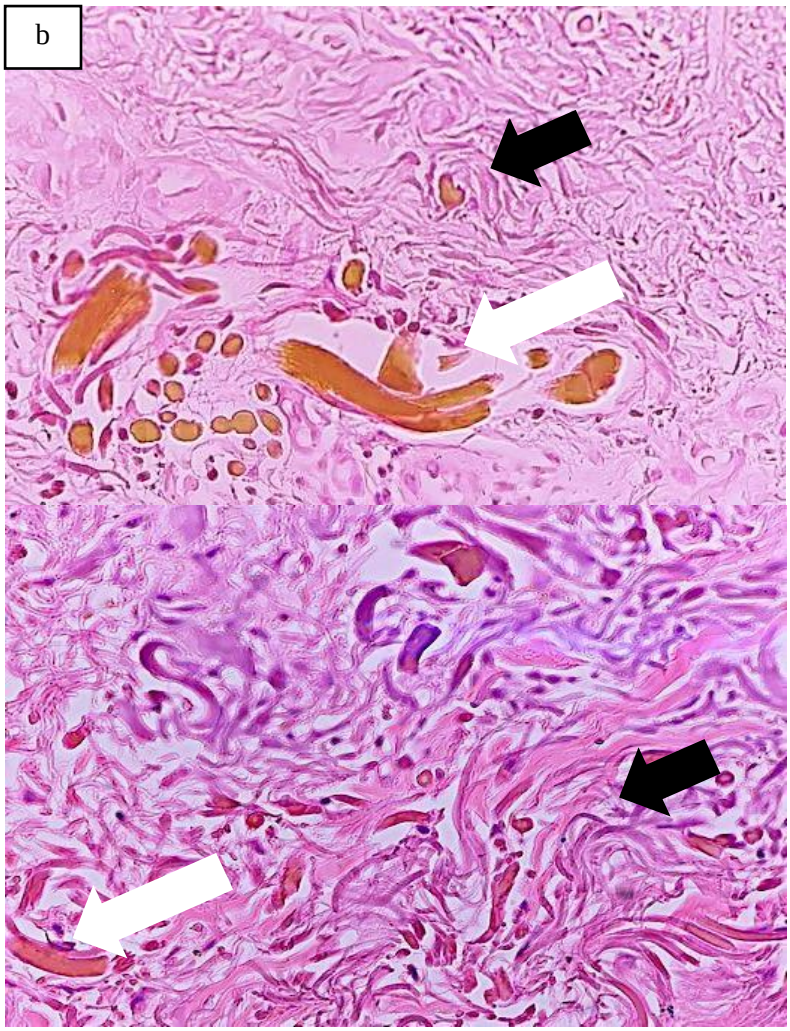

Figure 3b HPO view; Ochre colored bodies (white arrow), Solar elastosis (black arrow)

Many factors like UV exposure, prolonged use of hydroquinoine containing products, outdoor activities and amount of the product applied have been identified for a patient to develop EO [7]. Even at low concentrations of hydroquinoine (2%), EO has been reported. This occurrence was also found in our patients who used the 2% concentration. All of them did experience this untoward complication which implies that the concentration of hydroquinone may not be a key player in the development of EO. The presence and interplay of other factors mentioned might also be evident. A study in Asia purported that it is the extended use of hydroquinone that caused this condition more than its concentration [8]. Exogenous ochronosis is commonly seen in females due to hormonal factors that heighten their propensity for hyperpigmentation disorders such as melasma. An in vitro study showed that 17B estradiol concentrations in pregnancy and ethinyl estradiol which is often used in oral contraceptive pills, combined with UVB exposure were identified to increase melanin production leading to hyperpigmentation disorders [12]. Estradiol, leutinizing hormone and follicle- stimulating hormone levels were identified to be higher in women with melasma compared to those without [13]. This may explain the heightened use of topical lightening agents that lead to abuse and complications [6]. As all of our patients are Filipino who all reside in the Philippines which is a tropical country, daily UV exposure combined with hormonal influences might account for the demographic

data presented in this case series. Majority of our patients were female who used topical hydroquinoine containing whitening agents for a mean duration of 5.3 years without sun protection. Similar to the systematic review on hydroquinoine- associated ochronosis done in 2020, which reported that middle- aged women were majority of patients (53.2%) who used hydroquinoine for a mean duration of 5 years [14].

Clinically, exogenous ochronosis manifests as asympromatic gray-brown or blue-black macules on the cheeks, temples and neck [5]. However, during its early stages it may easily mimic melasma. Distinguishing between the two proves to be important as observed worsening of pigmentation may lead to increased application of lightening products that may worsen EO. Clinical clues such as, a patient's chronic use of hydroquinone, facial hyperpigmentation unresponsive to usual treatment, coarse texture of the skin, fine telangiectasia and hyperchromia with "speckling" are features that may alert us to screen the patient for exogenous ochronosis [15]. Clinching the correct diagnosis can help us manage patient expectations and outcomes. The gold standard for diagnosis remains to be a skin punch biopsy, however dermoscopy has been useful to identify peculiar findings in exogenous ochronosis that may help in securing the diagnosis [15, 16]. Large scale studies on dermoscopy findings of EO have not been done to the best of our knowledge. However, finding of typical blue- gray amorphous areas obliterating follicular openings have been reported in EO together with irregular brown-gray globular, annular and arciniform structures, worm-like structures and white dots. As opposed to finding dark brown reticular pattern-accentuation, sparing follicles and sweat gland openings in melasma [10, 15]. Our patient's clinical and dermoscopy presentation are very much similar to EO. Its presentation clinically as blue- gray in color is due to the pigment's location in the dermis (Tyndall effect). These findings in dermscopy correlates with the histology showing the yellow-brown or ochre banana-shaped fibers in the papillary dermis.

To date, there are still no treatment guidelines for exogenous ochronosis. Various therapeutic trials have been done however results have been varied. EO remains to be difficult to treat and early discontinuation of the offending agent, hydroquinone, is the cornerstone of management. Therefore, early diagnosis must be made in order to prevent worsening of lesions.

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Delayed Type Hypersensitivity Towards Cosmetic Hyaluronic Acid Dermal Filler: A Case Report

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Abstract

At the present time, the most common nonsurgical procedure in the aesthetic field are hyaluronic acid (HA) dermal fillers. It is appealing to many injectors as they are reversible with hyaluronidase and are generally well tolerated. However, there are several case studies which report hypersensitive reactions weeks after HA filler injections. The exact pathophysiology is inconclusive, but many agree that patients' biological factors, injection technique and variations in the properties of the fillers could potentially play a role. In this case report, we discuss our encounter with a 60-year-old Chinese lady who presented to us two weeks after lower face hyaluronic acid filler injections with generalised pruritic facial rash and oedema. A clinical diagnosis of atopic dermatitis was made and the symptoms resolved with systemic corticosteroids.

Keywords: Delayed hypersensitivity, Hyaluronic acid dermal fillers, Dermal filler injections

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In the aesthetic field, the most common nonsurgical procedure is dermal filler injections [1]. Dermal fillers, especially hyaluronic acid dermal fillers, are popular due to their ease of administration and ability to deliver the desired aesthetic benefit. There are four categories of dermal fillers according to FDA based on composition:

1. Hyaluronic acid which usually lasts between 6-12 months.
2. Calcium Hydroxylapatite – is a mineral found in bones. This material lasts up to 18 months.
3. Poly-L-lactic acid is a biodegradable synthetic material. These fillers may last up to two years.
4. Polymethylmethacrylate beads (PMMA) are the only filler that can't be absorbed by the body. They're only used around the mouth and the results are permanent.

Besides that, they can also be classified as temporary, semi-permanent, or permanent depending on the duration of time the filler remains in the tissue [2].

There are risks involved with the use of dermal fillers, most side effects reported in clinical trials and post-market surveillance occur shortly after injection and subside within a few weeks. In some cases, side effects may emerge weeks, months, or years later. Common risk includes, bruising, redness, swelling, pain, tenderness and itching and rashes. Serious problems are rare but can include:

- Infection
- A lumpy appearance under the skin, which might need to be treated with surgery or medicine.
- The filler moving away from the intended treatment area, need to be removed using surgery.
- Scarring
- Blocked blood vessels in the face, which can cause tissue death and permanent blindness.

Based on a study in the United States, hyaluronic acid (HA) fillers made up 78.3% of all injectable dermal fillers [1]. The compatibility of HA with the human body and the reversibility of injected HA via intralesional hyaluronidase enzyme make HA-based dermal fillers appealing to a large number of injectors. They are generally well tolerated, but as dermal filler demand increases, more problems are anticipated. Even in the hands of a skilled injector, complications may arise.

Most reported cases on delayed hypersensitivity are thought to be immunological in etiology, as all injected sites were concurrently affected [3]. It is impossible to predict, and it can occur in both people who have been injected before and those who have not [3]. The primary objective is to prevent them; however, it might not always be feasible. Adverse effects often linger as long as the filler remains in the skin, meaning that temporary fillers have short-term adverse effects while permanent fillers may generate lifelong adverse effects. Otherwise, infections must be prevented with the utmost care, and the injection technique must be precise to prevent further complications from occurring [4]. This report's purpose is to examine late-onset inflammatory reactions by discussing a case observed in an aesthetic clinic.

Case Presentation

Madam FSW, a 60-year-old Chinese lady presented with itchy, red and dry patches all over her face two weeks after injection of hyaluronic acid filler. Apart from underlying hypertension and dyslipidemia on medications, she has no known allergies towards any foods or drugs. At the encounter, she was comfortable and did not have any difficulty breathing. She was a subject during a lower face hyaluronic acid filler training in an aesthetic clinic two weeks prior to the skin eruption and that was her first time undergoing an invasive aesthetic procedure. She received a total of 3 ml of monophasic hyaluronic acid fillers during the

said procedure with 0.5 ml on each canine fossa, 0.5 ml on each side superficially over the wrinkles at the nasolabial folds, and 1.0 ml on her upper lip. The procedure was done under aseptic technique and was uneventful during as well as immediately post procedure for two weeks. Madam FSW did not recall eating anything out of the norm, and her skincare routine was not changed. There was also no change in household detergents and environment.

On examination, there were multiple erythematous, scaly, and pruritic polymorphic patches and macules scattered all over her face, most prominently over her forehead and bilateral cheeks. The lesions were not raised, and the borders were not defined. The largest patch measured 1.5 cm x 1.2 cm. The eruptions were only confined to the face and were not seen anywhere else on her body. Her face was notably oedematous as well. Her vital signs were normal and systemic review revealed no abnormalities. She was seen once at first encounter and was given one more appointment one week later to reassess her condition.

Management and Outcome

A clinical diagnosis of atopic dermatitis was made. Madam FSW was prescribed Topical Clobetasone Butyrate 0.05% Cream twice daily, Tablet Levocetirizine Dihydrochloride 20 mg BD and Tablet Prednisolone 10 mg BD for five days. Her symptoms resolved on day 2 of treatment and she has been well since the completion of treatment.

It is rather clear that the only thing she has been newly exposed to for the past few weeks was the monophasic hyaluronic acid filler injection. Thus, it is likely that it is a delayed hypersensitivity reaction from the product. This is further supported by her signs and symptoms resolving shortly after commencing treatment for atopic dermatitis. Figure 1, Figure 2, Figure 3 and Figure 4 show the picture of the patient before the hyaluronic acid filler injection, during presentation, close up pictures of the generalised facial rash and oedema and on day 2 of treatment with systemic and topical corticosteroids respectively.

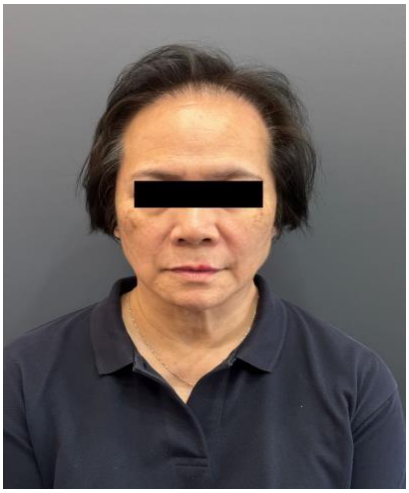

Figure 1 Picture taken before the hyaluronic acid filler injection 2 weeks prior to presentation

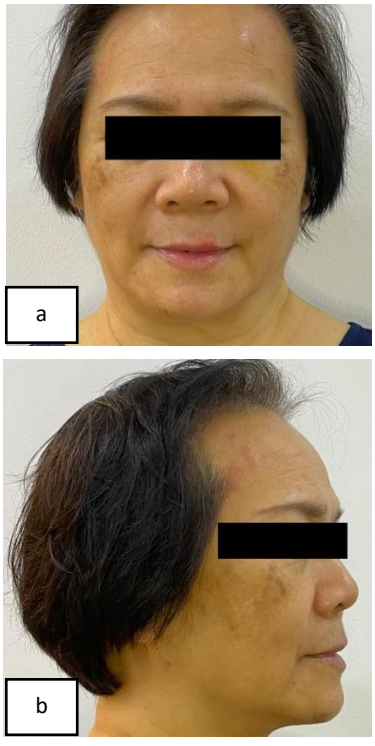

Figure 2 Pictures taken at presentation showing facial oedema and erythematous patches and macules all over the face, more pronounced over the forehead and bilateral cheeks at the nasolabial folds.

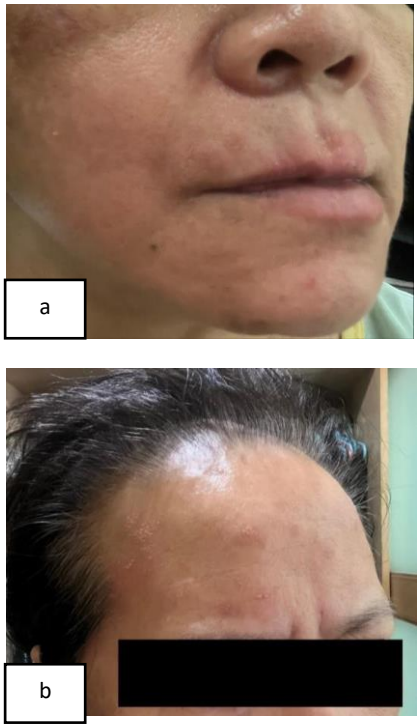

Figure 3: Close up pictures of the abovementioned generalised facial rash and oedema.

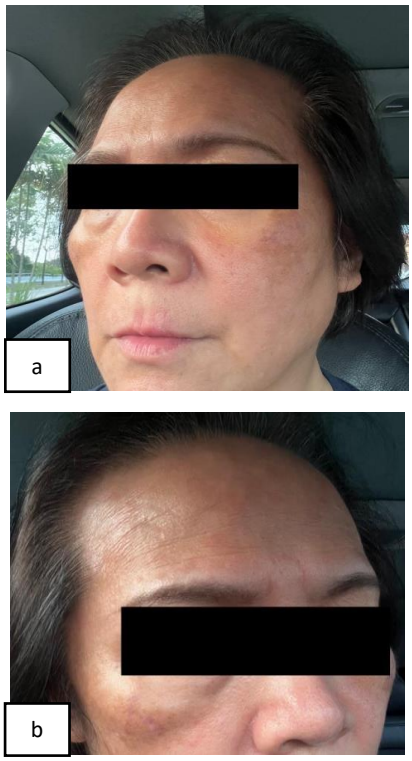

Figure 4: Pictures taken on day 2 of treatment with systemic and topical corticosteroids.

Discussion

Hypersensitivity can be broken down into four distinct subtypes; however, for the purposes of this discussion, we will focus on the fourth type which is the delayed type of hypersensitivity. Delayed type hypersensitivity (DTH) originates from a skin test for tuberculosis diagnosis, referring to the cellular infiltrates that cause induration and erythema at the skin test site within 24 to 72 hours. DTH initially explains the response to the tuberculosis skin test and to distinguish between antibody-mediated immediate and delayed cellular skin test results [5]. The definition of the term has now been broadened to cover skin reactions to chemicals and plants as well as cell-mediated responses to bacterial or fungal respiratory infections [5].

It is uncertain when delayed hypersensitivity may occur after an HA filler injection, as it can manifest from weeks to months later. Therefore, predicting the likelihood of its occurrence is not possible [6]. Multiple reports have been published in an attempt to understand the cause of delayed hypersensitivity amongst use of hyaluronic acid fillers [7, 8]. Several factors have been proposed as potential causes of the development of adverse reactions to HA fillers, including biological or patient-related factors (such as previous skin or systemic conditions like infections or trauma), injection technique (including filler volume, repeat treatments, and intramuscular injection), and variations in the properties of the fillers themselves [6].

Hyaluronic acid, a type of glycosaminoglycan, are generally non-immunogenic, as polysaccharide molecules that are found in them are identical to those that make up a significant portion of our skin. However, it is important to note that the presence of trace protein contamination or other constituents in the filler (such as cross linkers and conservati-ves) may potentially trigger an immune response [9]. This is further compounded by the rise of counterfeit and non-FDA approved products in the market in which more adversities are observed with the use of those products [10].

Commercially available fillers made with hyaluronic acid possess diverse properties, such as the extent of cross-linking and gel concentration, significantly influencing their clinical results. To comprehend the reasons behind delayed hypersensitivity reactions, it is crucial to understand these attributes. It should be emphasized that the factors causing such reactions are not solely determined by the properties of the hyaluronic acid fillers, but also by the reaction of the biological host.

The pathophysiology of delayed hypersensitivity towards hyaluronic acid fillers is not well understood, but is often observed in patients following a flu-like illness [3, 6, 11, 12]. It is believed that a systemic inflammatory response could speed up the breakdown of the filler, causing fragments of low molecular weight of hyaluronic acid to be immunogenic [8], especially since in vitro studies have shown that CD44 is a receptor through which hyaluronic acid activates T-lymphocytes [13]. When an allergen comes into contact with the skin, the pathophysiology of allergic contact dermatitis begins. Langerhans cells absorb this allergen when it reaches the stratum corneum of the skin [14, 15]. These cells then digest the antigens, which are then exhibited on their surfaces. Langerhans cells then proceed towards nearby lymph nodes. The T-lymphocytes nearby are exposed to the antigens that these cells have taken up. Thus, antigen-specific T cells are generated through the processes of clonal expansion and cytokine-induced proliferation. These lymphocytes may then enter the epidermis via the blood. The sensitization phase of allergic contact dermatitis is the aggregate name for this process. After a second exposure to the antigen, the elicitation phase starts. The interaction between the antigen-containing Langerhans cells and the T lymphocytes specific to that antigen causes cytokine-induced proliferation. In turn, this proliferation causes a focused inflammatory reaction.

In this report, we present a rare case of hypersensitivity reaction to hyaluronic acid dermal fillers that occurred after a 2-week period. This particular case was unique in that the skin eruptions were not limited only to the treated area but over her face generally, however, a flu-like prodrome is not observed in our patient in this case study, which raises more questions regarding the pathophysiology of the disease process.

The mechanism behind this delayed hypersensitivity reaction is not yet fully understood, however, its association is hypothesized due to the resolution of symptoms with systemic corticosteroids. One notable drawback of this article is the lack of histological analysis, which was not conducted as the patient preferred minimally invasive treatments for her symptoms with a speedy resolution. Consequently, biopsy was not performed. A similar Type 4 reaction to cosmetic filler following COVID-19 vaccination was observed as well in Canada [16].

Physicians can take certain preventive measures to minimize the risk of allergy. A detailed allergy history should always be included in every consultation. Identical hyaluronic acid filler that will be administered to the patient can be utilised to conduct an allergy work-up such as a skin allergy test. However, due to costing and limited sensitivity of these tests, even if the findings are negative, a hypersensitive reaction cannot be completely ruled out, making it difficult to draw firm conclusions from this test.

In conclusion, as the demand for and use of hyaluronic acid dermal fillers continues to rise across the country, it is imperative that medical professionals be vigilant regarding the possibility of complications when counselling patients and carrying out the treatment itself. Physicians should take the initiative to stay up-to-date with the latest research and guidelines

in this field and should always prioritize patient safety and well-being.

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Lichen Planus Pigmentosus and Concomitant Frontal Fibrosing Alopecia in A Filipino Woman: A Case Report

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Abstract

Facial hyperpigmentation and pigmentary lesions are often difficult to distinguish in skin of color. Hence, correlation of clinical, dermoscopy and histopathology is necessary to establish definite diagnosis. Lichen planus pigmentosus is a condition of unknown etiology which presents with ashy pigmentation on the exposed areas. Frontal fibrosing alopecia is an uncommon variant of lichen planopilaris and presents with progressive recession of the fronto-temporal line. To date, coexistence of lichen planus pigmentosus and frontal fibrosing alopecia in Filipinos has never been reported.

Keywords: Lichen Planus Pigmentosus, Frontal fibrosing alopecia, Pigmentary disorders, Dermoscopy

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Lichen planus is a condition that is found worldwide, with its incidence varying from 0.22% to 1% depending on the geographic location [1]. It can affect various areas, including the skin and mucous membranes such as the oral, vulvovaginal, esophageal, laryngeal, and conjunctival mucosa. Different variants of lichen planus exist, characterized by variations in lesion morphology and site of occurrence. These subtypes include popular (classic), hypertrophic, vesiculo-bullous, actinic, annular, atrophic, linear, follicular, and lichen planus pigmentosus (LPP) [2]. Lichen planus pigmentosus is a pigmentation disorder characterized by the presence of dark-brown to grey macules, primarily appearing in sun-exposed areas. While it predominantly affects women, unlike frontal fibrosing alopecia (FFA), it is more frequently observed in individuals with higher skin phototypes [3]. FFA is a type of primary cicatricial alopecia characterized by lymphocytic infiltration and is considered a variant of lichen planopilaris [4] that is characterized by the gradual recession of the hairline in the frontotemporal area. While it predominantly affects postmenopausal women, there have been reports of its occurrence in premenopausal women as well as in males [5].

Case Presentation

We present the case of a 54-year-old Filipino woman with Fitzpatrick Skin type IV-V, housewife, who sought consultation for hyperpigmented patches on cheeks and extensor surface of upper extremities and one-year history of frontotemporal hair loss. History of hyperpigmentation started two years prior to consultation, when she noted the appearance of few hyperpigmented macules and papules on the extensor surface of the arm, and no topical medications were applied. Lesions increased in size and number coalescing into multiple hyperpigmented patches and plaques accompanied by pruritus, now involving the face and V-neck line. One year later, gradual hair thinning on the frontotemporal area was noted. No history of chemical hair straighteners uses or illicit use of drugs or contact dermatitis. On examination, the patient had no medical illness and family history was also unremarkable. Upon dermatological examination, there was diffuse slate-gray pigmentation on forehead, cheeks, preauricular, perioral area (Figure 1a) and the neck (Figure 1b). Multiple well-defined irregularly shaped hyperpigmented plaques and flat-topped papules were noted on the extensor surface of upper extremities (Figure 1c). Examination of the scalp revealed focal thinning of hair on the frontotemporal area (Figure 1a).

Dermoscopy of the lesion on the extensor surface of arms showed dots and globules in a “hem-like pattern”, discrete bluish-gray deposits with occasional curvilinear distribution with sparing of follicular openings and accentuation of pigment around the follicular openings (Figure 2a) Dermoscopy of the scalp revealed irregularly distributed pinpoint white dots and absence of follicular ostia (Figure 2b) Skin punch biopsy was done on the face and the sections showed a basket woven stratum corneum with thinning of the epidermis and focal areas of vacuolar alteration of the basal cell layer. Some necrotic keratinocytes were seen. The dermis reveals civatte bodies and a mild superficial perivascular inflammatory infiltrate of lymphocytes (Figure 2c). Histologic examination of the scalp revealed a basket woven stratum corneum, thinning of the epidermis with focal areas of vacuolar alteration in the basal cell layer with necrotic keratinocytes. The dermis revealed fibrosis, numerous-pigment laden macrophages and perivascular and perifollicular inflammatory lymphohistiocytic infiltrate. (Figure 2d) Dermoscopy and histopathology findings were consistent with LPP and FFA respectively.

Fig.1 (a) Diffuse slate-gray pigmentation on forehead, cheeks, pre-auricular, perioral area Fig. (b) Diffuse slate-gray pigmentation on the neck Fig. (c) multiple well-defined irregularly shaped hyperpigmented plaques and flat-topped papules were noted on extensor surface of upper extremities and posterior surface of the thigh

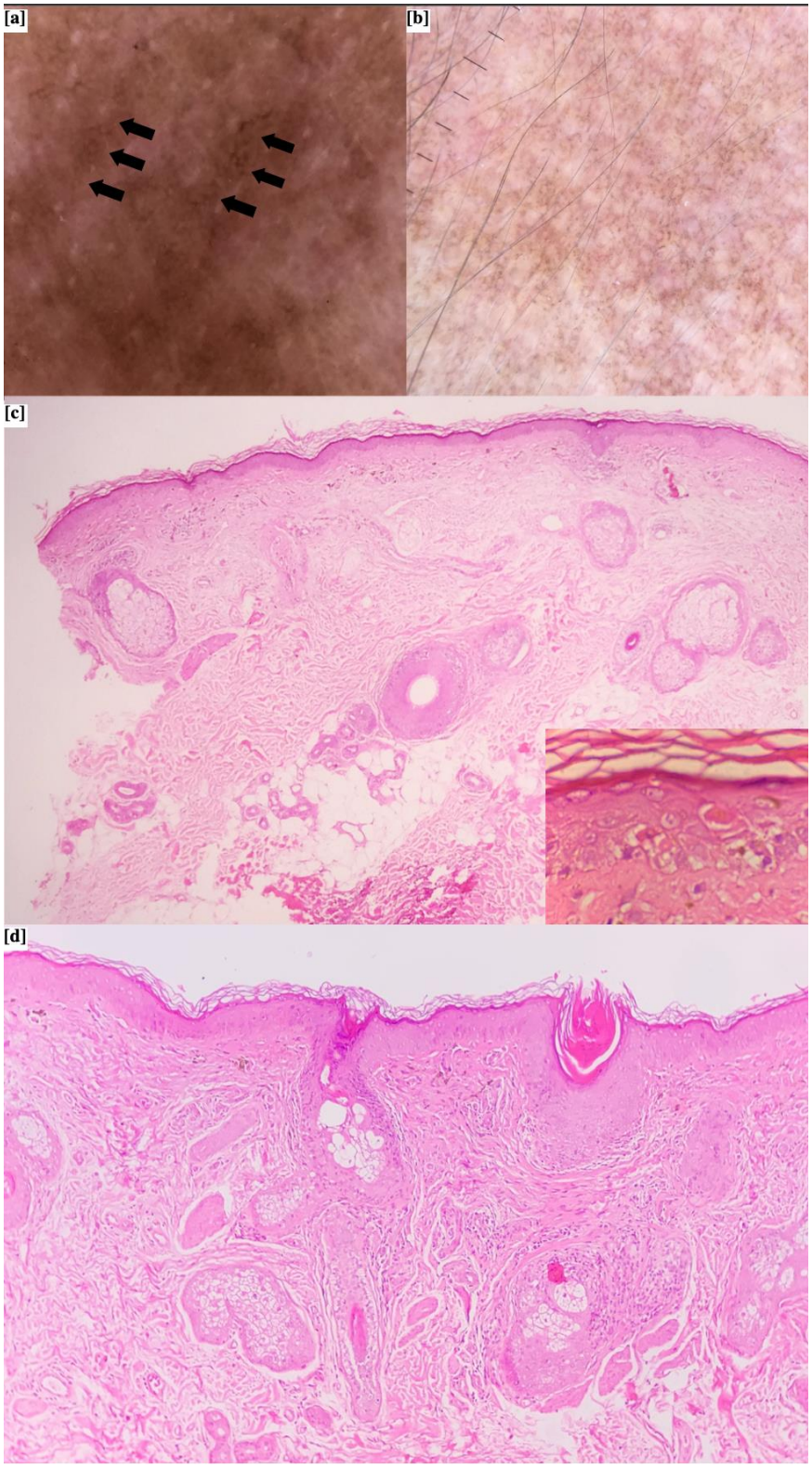

Fig. 2 (a) Dermoscopy of the lesion on the extensor surface of arms showed dots and globules in a “hem-like pattern” (black arrows) (b) Dermoscopy of the scalp revealed irregularly distributed pinpoint white dots and absence of follicular ostia. (c) Histopathological examination (HPE) of the skin from the face showed thinning of the epidermis and focal areas of basal cell layer vacuolar alteration. The dermis reveals civatte bodies and a mild superficial perivascular inflammatory infiltrate of lymphocytes. (d) HPE of the scalp revealed thinning of the epidermis with focal areas of basal cell layer vacuolar alteration with necrotic keratinocytes. The dermis revealed fibrosis, numerous-pigment laden macrophages and perivascular and perifollicular inflammatory lymphohistiocytic infiltrate (a,b Dermlite DL2x10 ; c, H&E, 10x; inset, 40x; d, H&E, 20x).

Discussion

The uniqueness of our case report lies in the rare coexistence of LPP and FFA in a 54-year-old Filipino woman with Fitzpatrick Skin type IV-V. LPP and FFA are two distinct clinical variants that fall within the broader spectrum of lichen planus [6]. The exact cause of the LPP is uncertain, and it is thought that immunological processes and exposure to certain chemical and physical agents, including sunlight, mustard oil, henna hair dye, and amla oil, may contribute significantly to the development of the condition [7].

Dots and globules in a "hem-like pattern", discrete bluish-gray deposits with occasional curvilinear distribution with sparing of follicular openings and accentuation of pigment around the follicular openings were the observed dermoscopic findings. It is difficult to differentiate using dermoscopy alone with its differential diagnosis such as ashy dermatosis and erythema dyschromicum perstans. In the global consensus statement by Kumaransinghe et al8, ashy dermatosis, erythema dyschromicum perstans, and LPP are in the spectrum of the condition called acquired macular pigmentation of uncertain etiology (MPUE). There should also be an erythematous border to definitely label a condition as erythema dyschromicum perstans which is not present in our patient. In addition, the consensus also stated that if there is any history of pruritus and clinical features of papules and plaques associated with pigmented lesions, the condition is unlikely to be ashy dermatosis. In contrast with other conditions, LPP lesions commonly affect the head and neck and exposed and non-sun-exposed areas [8]. The findings of dots and globules in a linear/hem pattern in our dermoscopy were similar to the findings of Devanda et al9. in their case series of 27 patients with LPP. While these dermoscopic findings are not specific to LPP alone, it can be a diagnostic clue in diagnosing this condition.

Skin punch biopsy was done on the face and the sections showed a basket woven stratum corneum with thinning of the epidermis and focal areas of vacuolar alteration of the basal cell layer. Some necrotic keratinocytes were seen. The dermis reveals civatte bodies, melanophages and a mild superficial perivascular inflammatory infiltrate of lymphocytes. (Figure 2d). Based on the consensus by Kumarasinghe et al8, histopathology of ashy dermatosis, erythema dyschromicum perstans and LPP may appear similar during some periods of the disease and that the melanophages in the dermis causes the ashy pigmentation in ashy dermatosis, erythema dyschromicum perstans, and LPP. Our findings were similar to that of the frequent histological findings of LPP described in the literature including perifollicular hyperkeratosis, atrophy with hydropic or vacuolar degeneration of the basal layer of the epidermis, and sparse lymphohistiocytic or lichenoid infiltrates along the dermis, along with pigmentary incontinence and the presence of melanophages [10].

Dermoscopy of the scalp in our patient revealed irregularly distributed pinpoint white dots which resemble empty follicles and absence of follicular ostia. It is generally accepted that FFA initially presents as a non-scarring condition, and early intervention may help restore the function of damaged hair follicles. Distinguishing this condition from androgenetic alopecia, traction alopecia, or alopecia areata solely based on scalp dermoscopy can be challenging. Based on the algorithm by Shim et al., the hair shaft abnormality should be checked first [11]. Our patient did not present with dermoscopic findings of tapering hairs also known as exclamation hairs, yellow dots and black dots which are diagnostic of alopecia areata. Also, alopecia would present with a small round to oval hairless patch which is not present in our patient hence the group ruled this entity out. Another differential diagnosis would be

traction alopecia. Based on our patient's history, there was no past history of using tight ponytails, bun or braids or use of chemicals or heat on her hair. In addition, dermoscopic findings of traction alopecia would reveal broken hair or black dots which are not present in our patient. The closest differential would be female pattern androgenetic alopecia which can be differentiated clinically as this would present with a "Christmas tree" pattern of diffuse hair loss at the middle of the hairline as compared with FFA which would present with symmetric and band-like hair loss involving the frontal hairline. The findings from the multicenter study conducted by the International Dermoscopy Society, which examined FFA using clinical and dermoscopic parameters, indicated that 93.6% (176 out of 188) of participants showed empty follicles, and 92% (173 out of 188) exhibited a lack of follicular ostia which is similar in our study [12]. It is challenging to differentiate androgenetic alopecia and FFA using a dermoscope due to the similarities in their dermoscopic findings hence performing a scalp biopsy to confirm the diagnosis in patients with pattern hair loss.

The histological examination of the scalp is demonstrated on Figure 2c. Histopathological confirmation is necessary for the diagnosis of FFA. Our study was similar with the findings of Rao et al. where the histopathological findings of their group revealed marked perifollicular fibrosis, lymphocytic inflammation in a lichenoid pattern around the infundibulum, isthmus, and follicle bulge, and a reduction in the number of follicles replaced by fibrous tracts [13].

The treatment of both LPP and FFA remains to be challenging. Managing LPP typically involves the application of topical medications such as steroids, immunomodulators, keratolytics, hydroquinone (with or without retinoic acid), azelaic acid, kojic acid, glycolic acid, vitamin A, and a 10% dimethyl-sulfoxide aqueous solution, among other options. However, the effectiveness of these treatments can vary significantly [7]. Our patient was prescribed topical steroids and topical calcineurin inhibitors. Patient was then lost to follow-up.

The treatment approach for FFA encompasses various strategies. These include the administration of chloroquine at a dosage of 200mg twice daily for a duration of 6-9 months, or the use of doxycycline as a systemic anti-inflammatory agent. Additionally, potent topical steroids, intralesional steroids (at a concentration of 4-8mg/ml), topical minoxidil, and topical calcineurin inhibitors are commonly employed. Some authors also recommend short courses of systemic steroids as part of the management plan [14]. In a retrospective cohort study by Panchaprateep et al15, up to 90% of their patients reported improved or stable FFA after receiving antiandrogen (finasteride or dutasteride) or antimalarial along with topical treatment. In patients unresponsive to steroids, antiandrogen and antimalarial, systemic immunosuppressive agents such as cyclosporine and mycophenolate mofetil are also possible treatment options for this condition [15]. Baseline laboratories prior to starting of an anti-malarial and topical minoxidil were advised to the patient but she was eventually lost to follow-up.

In a retrospective descriptive analytical study conducted by de Brito et al.16, involving 104 patients with FFA associated with LPP, the researchers concluded that LPP could serve as an indicator or warning sign for the development of FFA. Our own findings align with their study, as we also observed the presence of LPP preceded the onset of FFA.

In recent years, there has been a significant rise in the number of reported cases of FFA globally. The coexistence of LPP and FFA indicates that the underlying inflammatory process may have systemic implications beyond the scalp [17]. Furthermore, FFA can have a detrimental effect on patients' quality of life, leading to psychological distress. The

presence of LPP and/or other facial changes in association with FFA may further exacerbate its impact [18].

Conclusion

LPP, a rare variant of Lichen planus, is frequently associated with FFA. Dermoscopy is essential in diagnosing LPP and FFA especially in skin of color. Histopathology remains to be the gold standard in the diagnosis.

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Early Recognition of Vascular Complication Following Hyaluronic Acid Filler Injection to Prevent Inadvertent Tissue Necrosis: A Case Report

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Abstract

Aesthetic medicine is rapidly gaining wide popularity as a non-surgical method to boost one's outlook. In the facial region, hyaluronic acid dermal fillers are routinely utilised for augmentation of soft tissues. Aesthetic physicians must be familiar with the complications that may occur during their administration and the potential adverse reactions post-injection. Intravascular occlusion of dermal fillers by far reign at the top of the list of potential complications. As initial signs (e.g. the immediate blanching of the soft tissues and pain from vascular compromise) can be masked by the prior injection of local anaesthesia with epinephrine, it is key that physicians must familiarise themselves with the subsequent signs and symptoms as well. Recognising signs of vascular complications at all time intervals is essential in managing its morbidity and is directly linked to its overall severity. In vascular occlusion with hyaluronic acid dermal fillers, early intervention with hyaluronidase in key in mitigating the overall complexity and morbidity, providing the best outcome for the patient. Meticulous follow-up over the subsequent few days post-administration of dermal fillers, is of utmost importance to identify any delayed presentation of complications and to monitor recovery. We present a case of vessel occlusion post-hyaluronic acid dermal filler injection with resolution following early administration of hyaluronidase and follow-up with short review intervals.

Keywords: Hyaluronic acid filler, intravascular complication, tissue necrosis, hyaluronidase

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Aesthetic medicine is rapidly gaining wide acclaim and popularity with the introduction of various minimally invasive treatment modalities for a plethora of conditions to achieve a better overall appearance. Apart from the well documented botulinum toxin for reduction of rhytids, currently dermal fillers, skin boosters and different collagen-stimulating agents are steadily gaining greater traction by the public. Dermal fillers using different active components have been introduced by various manufacturers and countries, including hyaluronic acid, Calcium hydroxyapatite (CaHa), and Poly-ε-caprolactone-based dermal fillers, with the latter two suspended within carboxymethylcellulose hydrogel carriers. Dermal fillers are increasingly being used worldwide for non-surgical soft-tissue augmentation to address various aesthetic concerns such as age-related volume loss, acne scars, traumatic injuries, HIV-associated lipoatrophy, and rhytids, partially due to their impressive safety profiles.

As the usage of dermal fillers is increasing, the absolute number of complications will by proportion also increase. Even in the hands of the most experienced injectors, various complications can still occur. Although most of the complications are transient and mild (e.g. oedema, erythema, local ecchymosis, and nodule formation), there exists some irreversible adverse effects that can cause serious functional and aesthetic deficits, such as tissue ischemia and necrosis. The true incidence of these unwanted events has not been established, which could be due to of the lack of a universal reporting system and underreporting by clinicians [1].

Case Presentation

A 60-year-old Chinese lady presented to our clinic with a main concern of low nasal bridge. She had no previous history of nose surgery or other aesthetic procedure done to her nose and regional tissue prior to this visit. She has no known medical illness or history of allergens as well.

She was offered all minimally invasive nasal bridge augmentation procedures, including nose thread insertion and dermal filler injections. She at first opted for thread insertion. Four threads were inserted into her nasal bridge under local anaesthesia and was able to achieve a more prominent nasal bridge result. Relevant post-procedure care was done, and home care instructions were advised to her.

Six weeks later, she returned to our clinic wanting further augmentation of her nasal bridge (Figure 1). This time, she insisted on injecting dermal fillers for a more three-dimensional effect on her nose. After presenting to her all the different filler options, she chose to proceed with the hyaluronic filler. Pure Lignocaine was injected into her nasal tip and nasal bridge, and some time was allowed for the onset of anaesthesia. Hyaluronic acid filler was then administered via a 22-gauge cannula from the nasal tip towards the nasal bridge, under the nasalis muscle and above the nasal cartilage, in a retrograde fashion with micro boluses. Once half of the syringe was injected, the immediate effect was shown to the patient. Upon seeing the result, she requested for further elevation of the nasal bridge at the sub-intercanthal level. The filler was subsequently injected supra periosteal with a 23-gauge needle.

Following the injection, the patient complained of pain over the nasal bridge and tissue erythema was noted at the site of injection (Figure 2). Firm but gentle massage was done over the affected area to disperse the filler consistently for 5 minutes. The discomfort eventually subsided following tissue massage, but it was noted that the erythema persisted. She was observed for another 15 minutes to monitor her condition; however, it was noticed that the erythema progressively worsened and thus a diagnosis of vascular occlusion from the hyaluronic acid filler was made. Early intervention with hyaluronidase was hence immediately initiated.

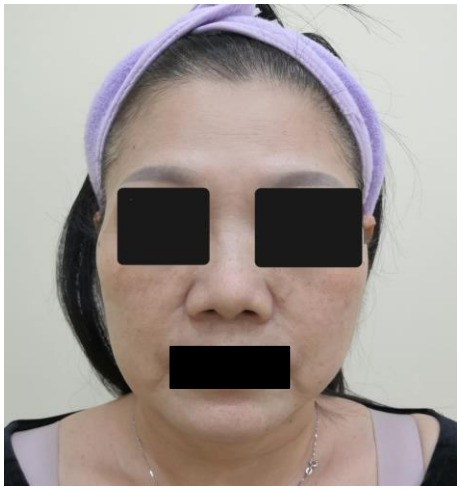

Figure 1 Prior to filler injection

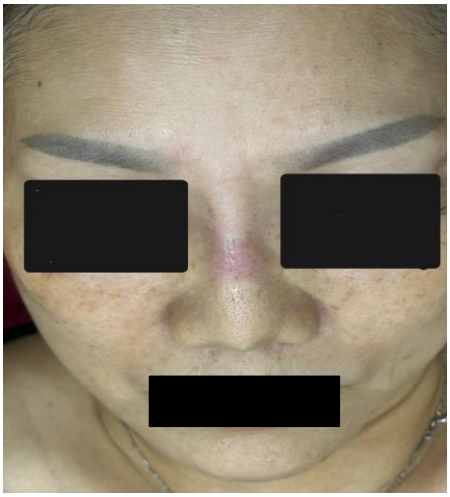

Figure 2 Immediately after filler injection

Management and Outcome

500IU hyaluronidase was injected into the erythematous area and thorough tissue massage was performed. After observation for 5 minutes, no improvement was observed, thus a second dose of 500IU hyaluronidase was injected again, followed by a third dose of 300IU hyaluronidase via a 22-gauge cannula to dissolve the entire column of hyaluronic acid filler. A prophylactic dose of IV Cefuroxime 1.5g was given intravenously as the patient was being identified as high risk for infection due to recent nose thread insertion. She was then monitored for another 30 minutes in our clinic with a reduction of the tissue erythema and discomfort. Surrounding tissues was warm and tissue capillary refill time was within normal range (Figure 3).

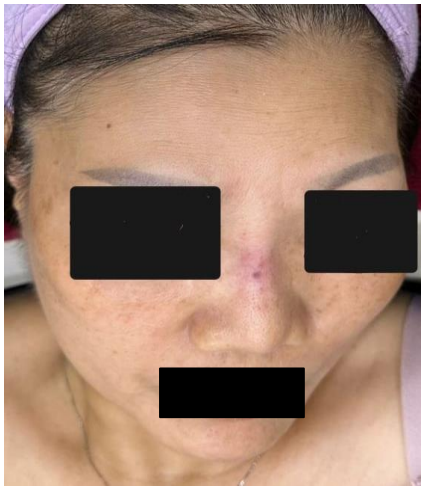

Figure 3 Post 500IU, 500 IU, 300IU Hyaluronidase injection

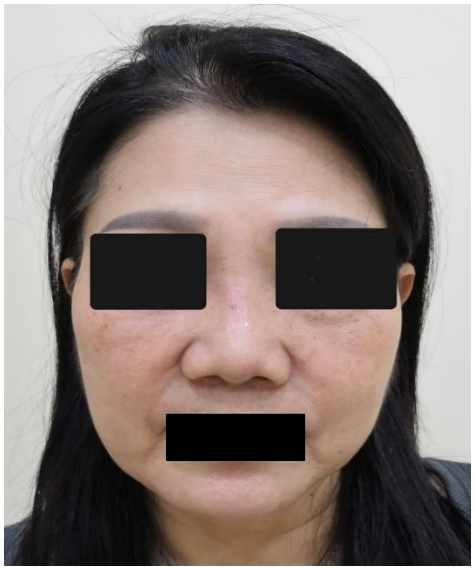

Figure 4 Follow up the next day

The patient was allowed to go home with Tab Cefuroxime 500mg BD for 4 days, Tab Prednisolone 10 mg OD for 5 days, and Tab Paracetamol 1g TDS for 5 days, Tab Papase I/I TDS for 5 days. On a follow-up appointment the next day, her condition was reviewed, and it was noted that her nasal bridge had returned to its previous state prior to the filler injection. She was free of pain and the tissue erythema was resolved (Figure 4). Continuous follow-up was done for the next 5 days and there was no further progression was noted.

Discussion

The success of facial dermal fillers is dependent on a variety of underlying factors. At the initial appointment, a thorough medical history of the patient should be obtained, including information on all prior surgical and aesthetic procedures as these can change the patient's baseline anatomy [2]. Patients who have previously had cosmetic surgery, such as rhinoplasty, may have unpredictable revascularisation and a delicate blood supply in the operated area, which may increase the risk of ischemia, necrosis, and vascular embolism after the filler injection [1].

While tissue ischemia resulting from dermal filler injections has been reported in various facial regions, certain areas of the face (e.g. the glabella, nose bridge and forehead) with extensive anastomoses between vascular territories, pose a higher morbidity of vascular occlusion due to the possibility of occluding adjoining smaller diameter vessels, for example, the central retinal artery. Additionally, areas with a limited source of collateral circulation also pose a higher risk, like the end arteries of the nasal tip and alar of the nose [3].

Signs and symptoms

The typical initial presentation of vascular compromise and occlusion is a disproportionate pain and marked tissue erythema from what is normally be expected from a routine injection. However, if local anaesthesia with epinephrine has been used either in combination with the hyaluronic acid or injected separately, the pain and erythema can be masked to an extent that in most cases, no significant pain or tissue erythema is perceived at all, until the anaesthesia wears off. Fillers containing adrenaline promote vessel constriction, thus lowering the risk of filler embolism. However, it may also obscure the blanching that occurs as a result of occlusion.

The skin changes in an arterial occlusion follow a relatively standardised trajectory that can be broadly categorised as Stages 1 to 5 [4].

Stage 1: Pallor and blanching: Typically manifests immediately and exhibits a pattern that corresponds to the pathway of restricted blood supply.

Stage 2: Livedo reticularis: Due to the build-up of deoxygenated blood within the venous network surrounding, occurs rapidly and usually lasts 24 - 36 hours.

Stage 3: Pustules form as a result of the overgrowth of Staphylococcus aureus. It usually occurs after 72 hours.

Stage 4: Coagulation: It may occur before Stage 3 or at the same time. Pustular overgrowth may mask tissue damage below, which in turn will mask the coagulation. It may take several days to gain visibility.

Stage 5a: The affected tissue will turn sloughy which is moist, creamy and yellow or green in colour.

Stage 5b: Eschar formation.

The inadvertent vessel occlusion from soft-tissue augmentation with dermal fillers can also result in severe complications, such as retinal artery occlusion and cerebral embolism, although very uncommon. Their signs and symptoms such as decreased visual acuity, orbital pain, headache, nausea, dizziness, or ptosis after the procedure, can indicate significant problems that require immediate attention. It is important to seek immediate ophthalmologic and/or neurological consultation if any of these symptoms are present.

Aspiration is often advocated as a method of avoiding intravascular injection: The appearance of blood in the syringe indicating the needle has entered a blood vessel [5]. Nevertheless, it is important to recognize that the lack of blood in the needle hub during aspiration does not ensure complete safety. The

reliability of aspiration test results is impacted by various factors such as the diameter and length of the needle, the type of syringe used, the size of the surrounding vessels and the rheological properties of the filler material [6]. As a result, it is misleading to make general statements about the dependability of aspiration, other than to assert that it may not be entirely reliable.

The utilisation of blunt cannulas can help reduce the likelihood of intravascular injection, however it is important to note that all cannulas, apart from the 10-gauge size, can still penetrate arteries and therefore is not entirely risk-free. An alternative option to minimise the risk of vascular compromise is to inject retrogradely while constantly moving the needle, which prevents the administration of a large deposit in a single area.

Treatment

Vascular occlusion needs to be treated promptly and effectively. In general, arterial occlusion is usually instantly evident. A complete halt of injections is necessary immediately. Warm compresses should be used to promote vasodilation coupled with a vigorous massage of the area to distribute the majority of the filler into surrounding tissues instead of entering the vessel. Additionally, topically applying a 2% nitroglycerine paste can be considered to promote further vasodilation to improve the circulation over the affected area [7].

Intralesional high-dose hyaluronidase remains the mainstay, immediate treatment for arterial obstruction and thromboembolism induced by hyaluronic acid injections [8]. Hyaluronidase is an enzyme that breaks down hyaluronic acid and is a crucial component of the extracellular matrix. Hyaluronidases were first identified in bacteria, and they are also found naturally in a variety of other organisms. In current practice, bovine and synthetic hyaluronidases are being used in medicine as adjuncts to improve the bioavailability of medications or to treat complications related to the injection of hyaluronic acid-based fillers for aesthetic purposes [9]. Hyaluronidases can be used therapeutically to minimize the appearance of nodules or lumps, as well as to treat excessive superficial infiltrations or overcorrections with hyaluronic filler augmentations.

High-dose pulsed hyaluronidase protocols states that the dose should increase consistently with the area of ischaemic tissue to be covered, as there is a minimum effective concentration of hyaluronidase for resolution. In this case, we are unable to identify the specific obstructed vessels and instead, we can only determine its clinical extent by analysing the capillary refill and the colour of the overlying skin [10]. Additional hyaluronidase should be injected (repeating 3–4 cycles) if an improvement is not visible within the first 60 minutes (such as less blanching and a less dusky or violaceous colour).

To attempt the development any further clots as a result of vascular impairment, the patient should be given an immediate dose of Tab Acetylsalicylic acid 300mg followed by 75mg daily until the vascular occlusion has resolved where there are no contraindications [11]. The patient should then be followed up daily to monitor for any improvement or worsening of their condition. Over the following few days, hyaluronidase injections and topical nitroglycerin paste can be continued as necessary according to the patient's clinical condition.

If severe necrosis is noted or there is delayed presentation of the patient in which the tissue is not healing well, hyperbaric oxygen therapy should be considered as another treatment option. Deep oxygen delivery into the skin using hyperbaric oxygen may help to maintain the viability of tissues. It is widely used to speed up wound healing when vascularity is compromised.

For post-treatment management, patients will need regular and intensive wound

care, adequate hydration, frequent proper wound debridement of dead skin, general supportive care, and infection surveillance to prevent worsening of their condition and with the hope of minimising scarring for the patient. Usually, patients who receive an immediate diagnosis and treatment within 24 hours tend to yield the best outcome. A delay in identification and treatment has been linked to varying degrees of skin loss, ulceration, and delayed healing, necessitating up to weeks of wound care and various degrees of scarring [12].

Conclusion

Even the most experienced dermal filler injectors can inadvertently administer fillers intravascularly and to confound matters, typical symptoms like pain or other classical signs might not present itself immediately. Regular, periodic checks should be routine for all patients receiving dermal filler therapy to screen for potential adverse reactions and to catch any said complications early on. In the event of intravascular hyaluronic acid dermal filler administration, early and effective intervention with hyaluronidase is the most predictable way to prevent unwanted outcomes such as tissue necrosis. More severe complications e.g. intravascular filler injection leading to blindness may not be salvageable and warrants rigorous further study. A thorough examination of the patient should be done prior to and after the treatment to ensure that the patient is reasonably safe from any complications before allowing them to leave the clinic in order to minimise delayed catastrophic incidents later.

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Efficacy of Low Fluence Q-Switched Nd:YAG Quickly Pulse to Pulse Mode (Q-PTP) 1064nm on Melasma: A Case Report

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Abstract

Melasma is a chronic acquired hypermelanosis of the skin that primarily affects women in Fitzpatrick skin types III-IV. The low-fluence Q-switched Nd:YAG laser has recently become quite popular for treating melasma This case report focuses on the treatment of melasma using low fluence Q-switched Nd:YAG Quickly pulse to pulse mode (Q-PTP) laser on a 43-year-old Fitzpatrick type III Chinese lady with a 10 year history of malar melasma. The patient underwent a total of eight laser treatment sessions at intervals of one to three months. The patient expressed satisfaction with the outcome, as the hyperpigmentation over both cheeks had noticeably diminished after the initial session. Q-switched Nd:YAG Quickly pulse-to-pulse mode (Q-PTP) laser at a wavelength of 1064 nm with low fluence reduced risk of exacerbation of melasma by inhibiting melanocyte activity through subcellular selective photothermolysis. The technique reduces the risk of cell death, inflammation, and damage to the basement membrane. Studies have also shown that laser toning can downregulate melanogenesis and melanogenic stimulators, resulting in the diminished function of melanocytes. Q-PTP uses two sub-pulses with brief intervals to create a larger peak power, lead to pressure changes and vibration of melanin, resulting in lesser pain, skin erythema post treatment and better patient acceptance. In conclusion, low fluence Q-switched Nd:YAG laser (PTP mode) has demonstrated efficacy in the treatment of melasma.

Keywords: Melasma, Q-switched Nd:YAG Quickly pulse to pulse mode (Q-PTP) laser, Fitzpatrick type III

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Melasma is a form of symmetrically distributed irregular brown macules on sun-exposed body parts, especially the face. Sun protection and topical lightening therapy are necessary for potential improvement in conjunction with techniques including chemical peels, intense pulsed light (IPL), fractional non-ablative lasers or radiofrequency, pigment lasers (microsecond, picosecond, Q-switched), and microneedling [1].

The Q-switched Nd:YAG laser is the preferred laser for treating mixed epidermal-dermal and dermal pigmented lesions, especially in those with dark skin. Effective targeting of dermal pigment is made possible by the laser's capacity to specifically target melanosomes in melanocytes, keratinocytes, and melanophages, as well as by its ultra-short pulse width (measured in nanoseconds) and configurable spot size.

The wavelength of a laser affects its selectivity and depth of penetration. The longer wavelength of the Q-switched Nd:YAG laser is 1064 nm, while the shorter wavelength is 532 nm. Due to its greater penetration and limited absorption by epidermal melanin, the longer wavelength of 1064 nm is appropriate for melasma. These lasers have a large spot size up to 10 mm, which also allows deep penetration of the laser beam. The mechanism of action of these lasers includes both a photothermal effect and photomechanical/photoacoustic phenomenon that is based on the principle of selective photothermolysis [2].

The low-fluence Q-switched Nd:YAG laser, particularly in Asia, has recently become quite popular for treating melasma. This technique involves multiple sessions at 1064 nm Q-switched Nd:YAG laser treatment with a collimated beam with a large spot size, low fluence (usually 0.8 and 2 J/cm2 depending on the spot size of the laser), and a frequency of 5–10 Hz. The endpoint of the procedure would be faint erythema. It is known to selectively destroy melanin in melanophores, whereas melanin-containing cells are left undamaged, resulting in safe depigmentation of melasma [3].

Quickly-pulse-to-pulse (Q-PTP) is the latest dual pulse mode Q-switched neodymium-doped yttrium aluminum garnet [QS Nd:YAG (QSNY)] laser technology. By producing a greater peak energy and more effective photo-mechanical destruction of melanin particles, Q-PTP enhances effectiveness and minimises negative effects [4].

This case report will be focusing on the treatment of melasma by using the therapeutic efficacy of low fluence Q-switched Nd:YAG Quickly pulse to pulse mode (Q-PTP) laser and their treatment outcome.

Case Presentation

A 43-year-old, Chinese lady, Fitzpatrick type III with no known medical illness, presented to our clinic with pigmentation over bilateral cheeks for 10 years. She claimed that she started noticing her pigmentations after giving birth of her eldest child and gradually worsened over the years. She started to feel insecure and having low self-esteem when her make up can no longer conceals her pigmentations.

She is a married lady and blessed with 2 children, who are 12-years old and 8-year-old respectively. She is an admin clerk and rarely involved in outdoor activities. She is compliant to her basic skin care products, like cleanser, toner, moisturiser. However, she only applied sunblock once daily and uses facial face occasionally. She has not received any depigmentation treatment prior this. There is no family history of similar complains.

On physical examination, there is irregular brown patches with ill-defined borders over bilateral malar region. She was diagnosed with malar melasma.

Management and Treatment

A single physician had treated the patient's complete face with laser therapy after getting

the patient's written informed permission. At treatment intervals ranging from one to three months, a total of eight laser treatment sessions were completed.

The patient had bilateral cheeks hyperpigmentation- melasma. Melasma area severity index (MASI) of 12.3 was graded during initial presentation. She had therapy with a Q-switched Nd:YAG Quickly pulse to pulse mode (Q-PTP) laser at a wavelength of 1064 nm. The fluence ranged from 0.70J/cm2 to 0.85J/cm2, with a spot size of 8mm, and the pulse rate was set at 10Hz (Table 1).

A picture of the patient was taken before and after each treatment session. The examination was carried out utilising standardised digital photography using an iPhone's camera in a predetermined photo corner of the room under same illumination. Throughout the process, the patient was asked if they experienced any pain or discomfort.

After 8 sessions of treatment, the patient was quite pleased with the results, noticing that the confluence of hyperpigmentation over both of her cheeks had been decreased to nearly non-visible compared to the first session. Apart for a minor prickling sensation during the process that was bearable without the need for any local anaesthesia, there were no severe side effects such as post-inflammatory hyperpigmentation (PIH) detected after the treatment.

Table 1: Parameters used in the laser treatment of patient's melasma using Q-switched (PTP) Nd:YAG laser 1064nm.

Session	Date	Mode	Spot Size (mm)	Fluence (J/cm2)	Pulse Rate (Hz)
1	26/5/2022	Q-switched (PTP) Nd:YAG 1064nm	8	0.85	10
2	27/6/2022	Q-switched (PTP) Nd:YAG 1064nm	8	0.85	10
3	25/7/2022	Q-switched (PTP) Nd:YAG 1064nm	8	0.85	10
4	29/8/2022	Q-switched (PTP) Nd:YAG 1064nm	8	0.9	10
5	15/11/2022	Q-switched (PTP) Nd:YAG 1064nm	8	0.8	10
6	13/12/2022	Q-switched (PTP) Nd:YAG 1064nm	8	0.8	10
7	11/1/2023	Q-switched (PTP) Nd:YAG 1064nm	8	0.8	10
8	8/2/2023	Q-switched (PTP) Nd:YAG 1064nm	8	0.75	10

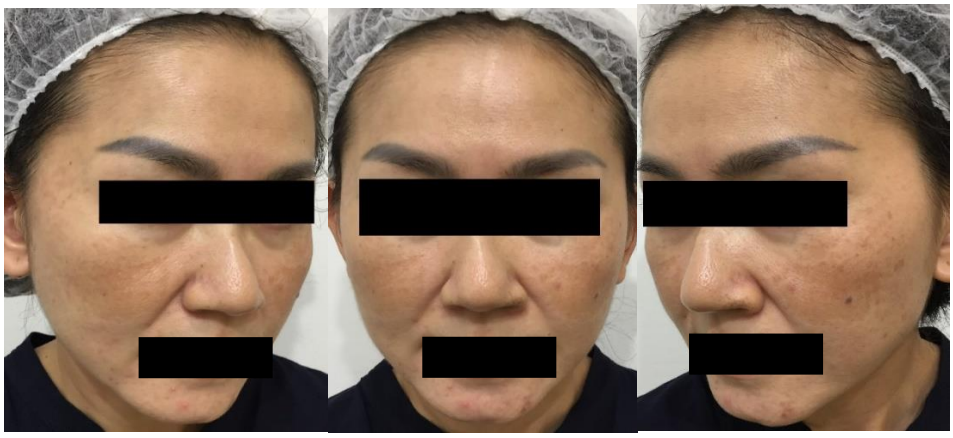

Figure 1: Right face (45 degree), front and left face (45 degree) view photos of patient during the first presentation.

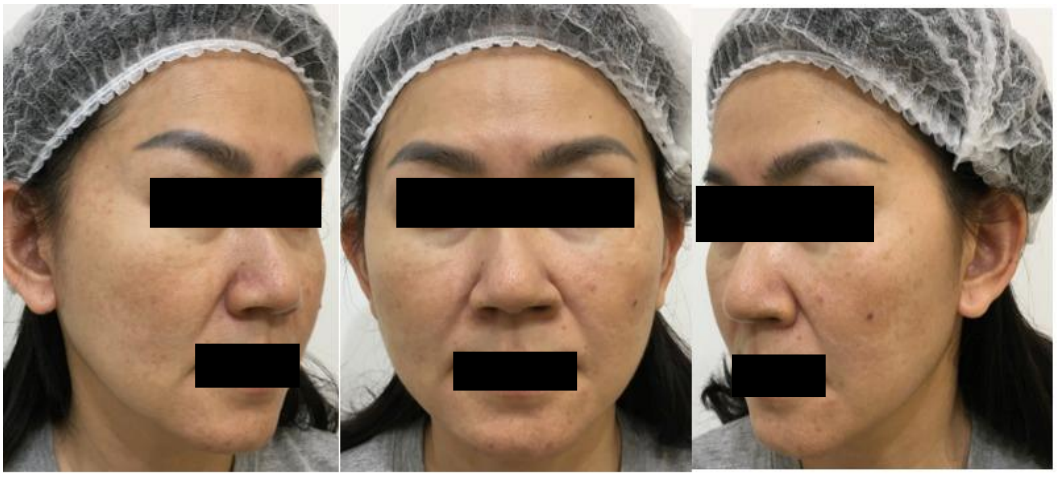

Figure 2: Right face (45 degree), front and left face (45 degree) view photos of patient after five sessions of treatment.

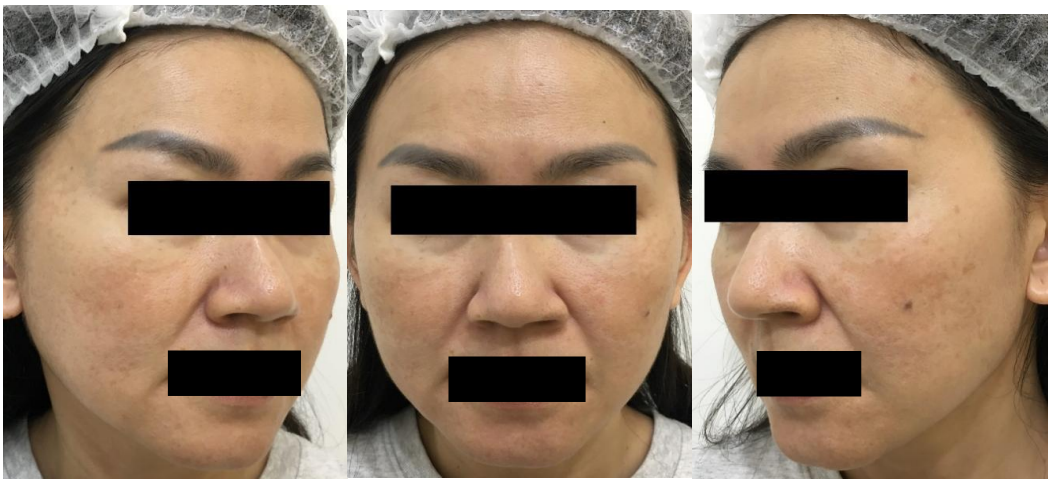

Figure 3: Right face (45 degree), front and left face (45 degree) view photos of patient after eight sessions of treatment.

Discussion

Melasma is an acquired hypermelanotic condition that manifests as irregular, light-to-dark, brown-colored macules on sun-exposed skin, particularly on the face. Though the condition is benign, it can cause significant negative impacts on individuals aesthetically and psychologically. It is classified into three types: epidermal, dermal, and mixed type. While epidermal melasma shows good response to topical treatments such as hydroquinone, tretinoin, glycolic acid, kojic acid, frequency-doubled neodymium-doped yttrium aluminium garnet (532 nm) laser, and intense pulsed light, such therapies are not effective for the dermal and mixed types of melasma that are prevalent in Asian populations.

In this study, we aimed to demonstrate the therapeutic efficacy of low-fluence Q-Switched neodymium-doped yttrium aluminium garnet (Nd:YAG) Quickly pulse-to-pulse (Q-PTP) mode laser on melasma. Q-switched Nd:YAG laser at 1064nm is the most used laser in the treatment of dermal and mixed type melasma because of its deeper penetrating properties and safety in pigmented skin.

This patient underwent 8 sessions of treatment with a Q-switched Nd:YAG (Q-PTP mode) laser at a wavelength of 1064nm with 3 passes at low fluence (ranged from 0.70J/cm2 to 0.85J/cm2). This method, also known as “laser toning”, was first proposed by Goldberg and Metzler in 1999, has gained popularity in treating melasma in the recent years due to its better outcome and lesser side effects in

comparison to high fluence Q-switched Nd:YAG laser.

The term "laser toning" originates from the improvements in skin tone that result from the use of the laser. The collimated top-hat beam, large spot size, ultra-short pulse duration, low-fluence, and multiple passes of Q-switched Nd:YAG laser are believed to cause minimal damage to the melanocytes. The traditional Q-switched Nd:YAG laser treatment, on the other hand, is based on the principle of selective photothermolysis, which uses a high fluence to destroy the pigment-containing cell. Due to presence of cell death, prostaglandins and proinflammatory cytokines will be released, thus resulting in inflammatory state and damage to basement membrane, leading to relapse, exacerbation of melasma, or pigmentary changes [5].

Several studies have shown that by going through the skin with multiple passes of low fluence Q-switched Nd:YAG laser, the melanosomes would heat up slowly and eventually be destroyed without damaging the melanocytes [6]. Moreover, the cell membrane and nucleus of the cell are kept intact and thus the cell death is avoided. Hence, it inhibits the melanocytes activity by a mechanism known as "subcellular selective photothermolysis" [5].

In a similar study by Kim et al[7], it is proposed that the downregulation of melanogenesis, tyrosinase, TRP-1, and TRP-2 may be responsible for the diminished function of melanocytes. Melanogenic stimulators, including a-MSH and NGF, were also reduced. Consequently, in the absence of cell death and heating of skin kept to a minimum, low fluence Q-switched Nd:YAG laser has not only demonstrated a more superior results in treating melasma compared to the traditional Q-switched Nd:YAG, but also a reduced risk in exacerbation of melasma.

Q-PTP is the latest dual-pulse mode Q-switched Nd:YAG lasers technology in which one pulse is split into successive two sub-pulses by extremely brief intervals in the Q-switched Nd:YAG laser technology, and two relatively weak energy pulses are accumulated from photoacoustic to photothermal to create a larger peak power than the existing single-pulsed Q-switched Nd:YAG lasers. Synergistic dual pulse immediately led to pressure changes and vibration of melanin, and peak energy was accumulated to increase the temperature of the targets. In the study by Guo et al[4] which compared the advantages, efficacy, and safety between laser toning with Q-PTP mode and single-pulsed mode in treating melasma in Chinese patients, showed that there was no significant difference in the treatment outcome with the same treatment parameters. However, a minor procedural pain experience, lesser skin erythema reaction post-treatment and better patient acceptance with Q-PTP mode demonstrated greater treatment safety and superiority than single-pulsed Q-switched Nd:YAG laser.

In conclusion, our data suggested that low fluence Q-Switched Nd:YAG laser (Q-PTP mode) can be used in treatment for melasma to achieve a satisfactory result in lightening of the pigments with low risk of side effects.

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Efficacy of Ablative CO_2 Laser In The Treatment of Xanthelasma Palpebrarum: A Case Report

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Abstract

Xanthelasma are yellowish plaque on or near the eyelids, more common seen in women and those of Asian or Mediterranean descent. Anyone is susceptible to xanthelasma however the risk of developing xanthelasma is higher in those who are overweight or hyperlipidemic. Classical treatment option remain surgical excision, alternatively in our setting, chemical peel utilizing Trichloroacetic acid (TCA) and laser treatment using carbon dioxide, erbium, pulsed dye, argon, and Nd:YAG lasers can be used to treat xanthelasma palpebrarum. We hereby present a case of a 52-year-old Malay gentleman, who had 10 years history of yellowish plaque over inferonasal region of bilateral eyes. He was successfully treated with a single session of CO2 ablative laser under local anesthesia for total removal of yellowish plaque following the diagnosis made based on his clinical presentation. In conclusion, CO2 ablative lasers are effective in treatment for total removal of yellowish plaque within one session.

Keywords: xanthelasma plapebrarum, laser, Q-switched NdYAG,

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Xanthelasma is a lipid-rich deposition, mainly cholesterol that are commonly found near or on the eyelid, known as xanthelasma palpebrarum. It is characterized by semisolid yellowish papules and plaques that occurs more commonly at the inner canthus of the eyelids that can be treated by multiple methods. Surgical excision has been the treatment of choice for decades but not without the risk of side effect like ectropion. Other modalities like the use of cryosurgery, radiofrequency, chemical cautery utilizing trichloroacetic acid have shown mixed result often requiring multiple sessions and frequent recurrence [1,2]. The use of ablative and non-ablative laser has become popular which minimizes sequelae and recurrence. This case report will be focusing on the treatment of xanthelasma palpebrarum with ablative carbon dioxide laser.

Case Presentation

A 52y.o. Malay gentleman with no known medical illness, presented to the clinic with 10years of asymptomatic, multiple, painless, slow progressive, non-pruritic, elevated, yellowish plaque over inferonasal region of bilateral eyes. He did not seek medical attention previously as he wasn't disturbed by the appearance of these yellowish plaque however, he had started focusing on his skin health after retiring recently. He was otherwise healthy until 3 years ago whereby he was verbally informed to have mild elevated cholesterol levels during his health screening with blood investigations. He was then advised for a healthy lifestyle modification along with diet change.

On examination, there were multiple yellowish plaques that varies in sizes over the inferonasal region of both eyes. Right lower eye lid has 2 plaques measuring 0.4 x 0.3cm and 1.0 x 0.3cm, adjacent to one another. Left lower eyelid has 1 larger plaque measuring 0.7 x 1.3cm. Based on the history and presentation of the lesion, a clinical diagnosis of Xanthelasma Palpebrarum was made.

Management

The procedure was explained to the patient and informed consent was taken. He was treated with single treatment session with Pulse Carbon Dioxide ablative laser under local anaesthesia. Carbon Dioxide Laser (10600nm) setting were pulse mode, with power of 6Watts and 20 -90ms. Total removal of yellowish fatty tissue and

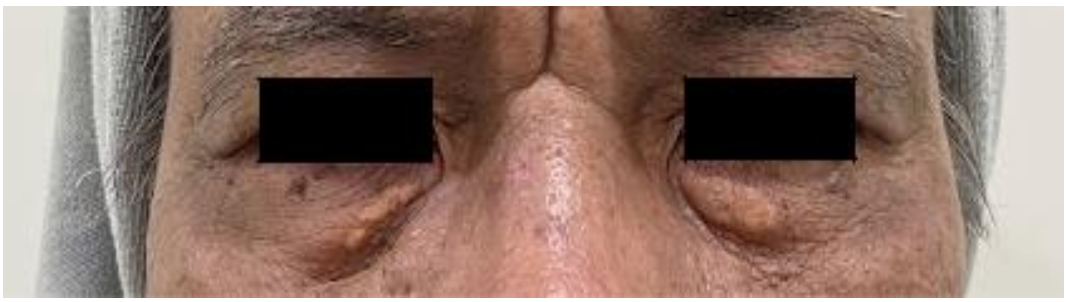

Figure 1: Location of the lesion

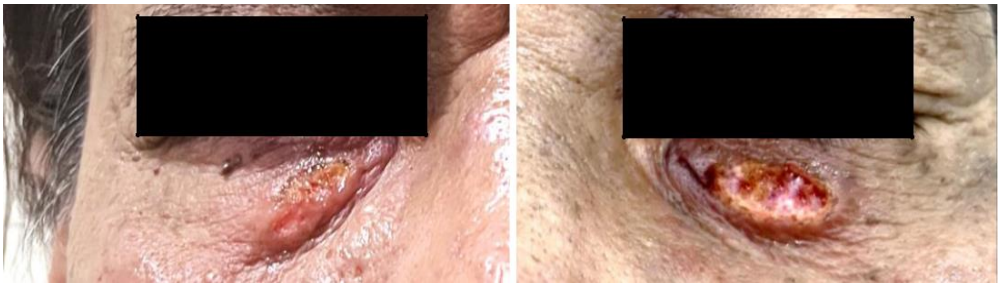

Figure 2: Pictures taken immediately after procedure. (a) Right; (b) Left

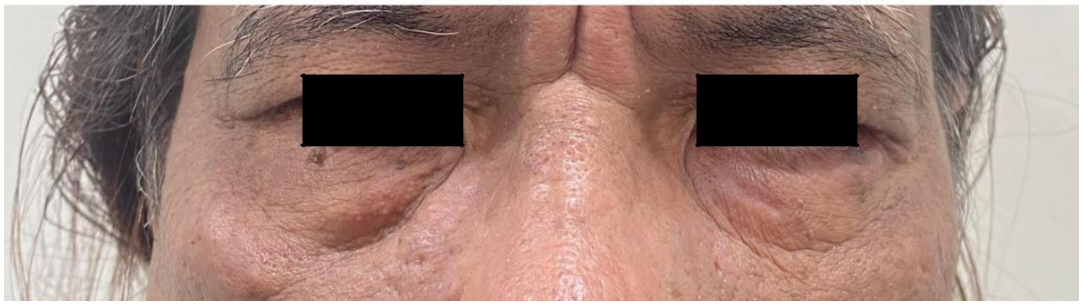

Figure 3: Picture taken 3 weeks after procedure.

appearance of underlying pink tissue was taken as endpoint of therapy. Mupirocin ointment was applied post procedure and he was asked to continue topical application twice daily till scabbing. He was instructed to keep the area clean and dry.

Outcome

Immediately post treatment, there were ulcerated lesions seen over the treated areas with no bleeding (Figure 2). After 3 weeks, he was reviewed to the clinic and the previous ulcerations was heal with no sign of scarring (Figure 3). After 4 months of procedure, the patient was followed up on and there was no sign of recurrence or scarring at the area of interest.

Discussion

Xanthelasma appears as yellow flat plaques over upper/lower eyelids, usually close to the inner canthus. The prevalence is estimated at 4% [3], with peaks seen in the fourth and fifth decades. It is more frequent in women and its prevalence increases with age. In many cases, it can be associated with an underlying dyslipidaemia. Histologically, xanthelasma represents lipid laden macrophages that are found in the superficial and mid-dermis [4].

Dyslipidaemia that presents with xanthelasma can stem from primary causes such as familial hypercholesterolaemia, or secondary causes such as obesity, diabetes mellitus, cholestatic liver disease, nephrotic syndrome, and certain medications [5]. However, xanthelasma may also occur in people with normal levels of circulating lipids. Even though xanthelasma is a clinical diagnosis, investigations are performed to rule out any associated primary or secondary dyslipidaemia. These include fasting lipid profile, fasting blood glucose, liver, thyroid and renal function tests.

The management of xanthelasma includes treating the associated dyslipidaemia, if there is any. Medical management includes lifestyle modifications such as regular exercise and low-fat diet, as well as lipid-lowering drugs. Although significant in the overall care of a patient with abnormal lipids, medical management has a limited role in the treatment of xanthelasma. There is no cutaneous complication that occurs with xanthelasma, and patients are often asymptomatic. However, treatment for its removal is still regularly sought for cosmetic purpose, as improving the dyslipidaemia does not always guarantee a regression of the xanthelasma. There is limited evidence in the literature that outlines the efficacy and safety of different treatment modalities for the removal of xanthelasma. Commonly cited treatments for xanthelasma removal include topical trichloroacetic acid (TCA), laser ablation and surgical excision.

Topical application of TCA 70% has been reported to be effective and well tolerated for flat plaques [6], whereas for papulonodular plaques, a higher concentration of TCA 100% was the most efficacious [7]. Overall, TCA treatment was found to be appropriate for smaller lesions, as larger lesions would require repeated procedures, and hence would result in

higher risk of pigmentation and scarring [8]. Post-inflammatory hyperpigmentation was reported at a rate of 9% - 12.5%, whereas hypopigmentation was reported at a rate of 21.5% - 33.4% [7,9]. Current literature also report recurrence between 25% - 39% [7,8].

Surgical excision has been used traditionally and often yields good cosmetic outcomes. Recurrence, however, is common and is reported to be as high as 40%-60% [10]. Therefore, it is usually advocated only for lesions involving the deep dermis or lesions infiltrating into underlying muscle. Laser ablation is an option that can be used to treat xanthelasma. The mechanism of action is said to involve destruction of lipid-laden macrophages via thermal energy, as well as coagulation of dermal vessels that prevent further lipid leakage into tissue to reduce recurrence. An array of lasers have been described in the literature, including CO2 and Er:YAG.

CO2 lasers target water, causing vaporization of water within cells and resulting in ablation of skin. There have been several studies employing CO2 laser to treat xanthelasma, majority of which report complete initial resolution. Raulin et al conducted a case series of 23 patients receiving high energy ultrapulsed CO2 laser therapy. The ultrapulsed CO2 enabled vaporization of a thin layer of tissue with sufficient thermal relaxation of surrounding tissue. All lesions could be completely removed with a single treatment, with only transient pigmentary changes (4% hyperpigmentation, 13% hypopigmentation) as side effects. No visible scarring occurred. Only three patients (13%) developed a recurrence of xanthelasma at the 10-month follow-up [11]. The efficacy and safety of super-pulsed versus fractional co2 laser treatment was compared by Esmat et al in a prospective randomised study of 20 patients. Results showed that a single session of ablative superpulsed co2 showed a more significant improvement of xanthelasma, compared to 3-5 sessions of monthly ablative fractional co2. However, side effects such as scarring, and recurrence were also more likely to occur [12].

Goel et al compared the efficacy of 30% TCA versus co2 laser in the treatment of xanthelasma in 50 patients. He concluded that both treatments were appropriate for clinically milder lesions. However, co2 laser was more superior than TCA 30% for severe lesions, as the study revealed that complete clearance was attained by the laser group, as opposed to only a 56% clearance rate for the TCA 30% group [13]. Co2 laser is likely to be more effective in these cases due to the associated coagulative effect that spreads beyond the ablative zone.

The Er: YAG is an ablative laser, with a smaller thermal coagulation zone compared to the co2 laser. Er: YAG has also been demonstrated to be successful in treating xanthelasma. It is reported have a faster healing time and lower risk of postinflammatory hypo- and hyperpigmentation compared to the co2 laser [14,15]. However, Lieb et al concluded that co2 laser was better suited to treat deeper lesions due to its hemostatic property [16]. Other lasers such as the Q-switched Nd: YAG, argon laser and KTP have also been employed to treat xanthelasma. Most of these lasers require multiple sessions with varying rates of clearance of lesions and recurrence. A review of a few case reports by Fusade, Karsai et al, Basar et al, shows that these lasers were less likely to achieve complete clearance of xanthelasma with a single session [17,18,19].

Conclusion

Despite being a relatively benign condition, which causes no functional problems, xanthelasma may cause significant psychological distress and treatment is very often sought for cosmetic reasons. It may also indicate an underlying dyslipidaemia, hence patients should be screened and managed

accordingly. There are multiple treatment modalities but there is currently no gold standard long-term treatment option, and recurrence is often seen with all therapeutic modalities.

In conclusion, our case report supports the safety and efficacy of a single session of CO2 laser for the removal of xanthelasma. To monitor for any recurrence of xanthelasma, patients will undergo periodic follow-up examinations (4 months, 6 months, and 12 months).

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Photographic, Dermoscopic and Histopathological Findings in A Case of Severe Acanthosis Nigricans and Phymatous Rosacea in A 51-Year-Old Filipino Man : A Case Report

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Abstract

Establishing a definite diagnosis for facial hyperpigmentation and pigmentary lesions in skin of color often poses challenges as they are frequently difficult to differentiate. Therefore, it becomes necessary to correlate history, clinical findings, dermoscopy, and histopathology to accurately identify and diagnose these conditions. We report a case of a 51-year-old Filipino man with a six-year history of asymptomatic pigmentation with a rough surface on forehead, cheeks, chin and neck. He also reported enlargement of the nose, earlobes, glabellar area and the chin. Dermoscopy and histopathology confirmed the diagnosis of acanthosis nigricans and phymatous rosacea. The coexistence of severe acanthosis nigricans and phymatous rosacea in skin of color has rarely been reported.

Keywords: acanthosis nigricans, rosacea, pigmentary disorders, dermoscopy

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"Dark spots on the face", "dark neck" and "dark underarms" are some of the aesthetic concerns of majority of the Filipinos. Acanthosis nigricans (AN) is rarely described among Filipinos since most of them have brown to dark-brown skin color. Acanthosis nigricans presents clinically with thickened hyperpigmented leathery plaques typically on the neck, intertriginous areas and the face. Usually, AN is a common dermatological manifestation associated with obesity, insulin resistance, endocrine disorders and internal malignancy.

Previously recognized as a chronic inflammatory skin condition, rosacea is now understood to be more than just a dermatological disorder. It is considered a systemic inflammatory disease that can affect multiple systems in the body. The original standard classification of rosacea identified the most common parts observed and it classified into four subtypes: erythematotelangiectatic, papulopustular, phymatous or ocular. While this classification is well known, it offers limited considerations as to the full spectrum of signs and symptoms of this condition. Current guidelines from the 2017 National Rosacea Society (Table 1) recommend a phenotype driven approach. The presence of either fixed centrofacial erythema that may intensify periodically or phymatous changes are already diagnostic criteria for rosacea. In the absence of these features, presence of two or more major phenotypes such as papules/pustules, flushing and facial telangiectasia may be necessary to establish the diagnosis. Ocular manifestations such as lid margin telangiectasia, conjunctival injection may also be considered as major features of rosacea [1, 2]. Previous studies have highlighted the association between rosacea and various systemic conditions, including cardiovascular diseases, metabolic syndrome (MS), and insulin resistance.

Case Presentation

We present the case of a 51-year-old Filipino man with Fitzpatrick skin type IV with a six-year history of asymptomatic dark brown to black-colored macular pigmentation on forehead, cheeks, chin and neck. The lesions had ill-defined borders and a velvety surface. Few years later, the enlargement of nose, chin, glabellar and earlobe were noted. The patient was initially diagnosed as lepromatous type of leprosy due to the appearance of leonine facies and referred to us for further evaluation. Our patient denies any previous history of dermatoses, trauma, local topical application, or systemic medication that could cause discoloration and no known history of malignancy. The patient has a medical history of hypertension and diabetes which require treatment. Additionally, he has a strong family history of hypertension, diabetes, and dyslipidemia. During the physical examination, elevated BMI and blood pressure were noted. Dermatological examination revealed hyperpigmented velvety thickening of the skin on the left cheek (Figure 1a), face (Figure 1b), right cheek (Figure 1c), metophyma (Figure 1d), gnatophyma (Figure 1e), neck (Figure 1i) and knuckles (Figure 1j). Rhinophyma (Figure 1g) and otophyma (Figure 1f and 1h) were also observed. The patient also had blepharophyma.

Based on the World Health Organization guidelines [3], a leprosy case is a patient having one or more of the following: 1) Hypopigmented skin lesions with loss of sensation, 2) impairment or involvement of the peripheral nerves as demonstrated by; a) definite loss of sensation or b) weakness of hands/feet or face or c) autonomic function disorders such as anhidrosis or d) presence of visible deformities, and 3) signs of the disease with demonstrated presence of bacilli in skin smear or histopathological confirmation. While our patient was presented with visible deformities, his neurological examination revealed intact sensation bilaterally without motor deficits bilaterally.

In all cases, the authors performed dermoscopy using a manual polarized light device (Dermlite DL2x10; 3Gen, San Juan Capistrano, CA). Dermoscopy of the cheeks (Figure 2a) demonstrated bluish gray areas with telangiectasias. Dermoscopy of the chin (Figure 2b) revealed prominent sulci, with larger brown globules and thickened perifollicular hyperpigmentation. Dermoscopy of the nape (Figure 2c) revealed markedly depressed sulci.

A 4mm skin punch biopsy of the left cheek (Figure 3a) revealed parakeratosis of the stratum corneum. There is acanthosis of the epidermis, hypergranulosis and mild spongiosis. The dermis reveals prominent fibrosis and enlarged sebaceous lobules. Fibrosis was also seen in the lower dermis. A 3mm skin punch biopsy on the left earlobe (Figure 3b) revealed mild acanthosis of the epidermis with basal cell layer hyperpigmentation. The dermis reveals fibrosis and enlarged sebaceous lobules. Fibrosis was seen in the lower dermis. Fite-Faraco stain revealed absence of acid-fast bacilli. Based on the correlation of the clinical, dermoscopic and histopathological findings, the diagnosis of AN and phymatous rosacea were made.

Management and Outcome

Patient was co-managed with a cardiologist and an endocrinologist for control of hypertension and diabetes respectively. He was prescribed with gel cream preparation containing a combination of the following: vegetable extracts (butcher's-broom, centella asiatica, calendula offinalis, horse-chestnut, liquorice), vitamin B3, betaine and β-glycyrrhetinic acid, sunscreen and low-dose oral isotretinoin (10mgs once a day for 1 month, 10mgs every other day for the 2nd month and 10mgs twice a week for the 3rd month) for the acanthosis and rosacea. In addition to the topical and oral medications, he underwent every 2 weeks of treatment with yellow laser 577nm (Quadrostar Pro®, Germany) using the following parameters; fluence: 15 J/cm2, pulse width: 36ms, pulse duration 1.5 sec, scanner mode 80% coverage) for a total of 6 sessions with remarkable improvement (Figure 4). He was also advised with strict sun protection and avoidance of rosacea triggers.

Table 1: Updated rosacea diagnosis and classification[1]

DIAGNOSTIC PHENOTYPES (only one required)	**MAJOR PHENOTYPES (any two required)**	**SECONDARY PHENOTYPES**
1. Persistent centrofacial erythema 2. Phyma; Rhinophyma Metophyma Otophyma Gnatophyma Blepharophyma	1. Transient facial erythema 2. Inflammatory papules/ pustules 3. Telangiectasias* 4. Ocular features *Excludes solely nasal alar telangiectasias	1. Burning 2. Erythema 2. Edema 3. Dryness

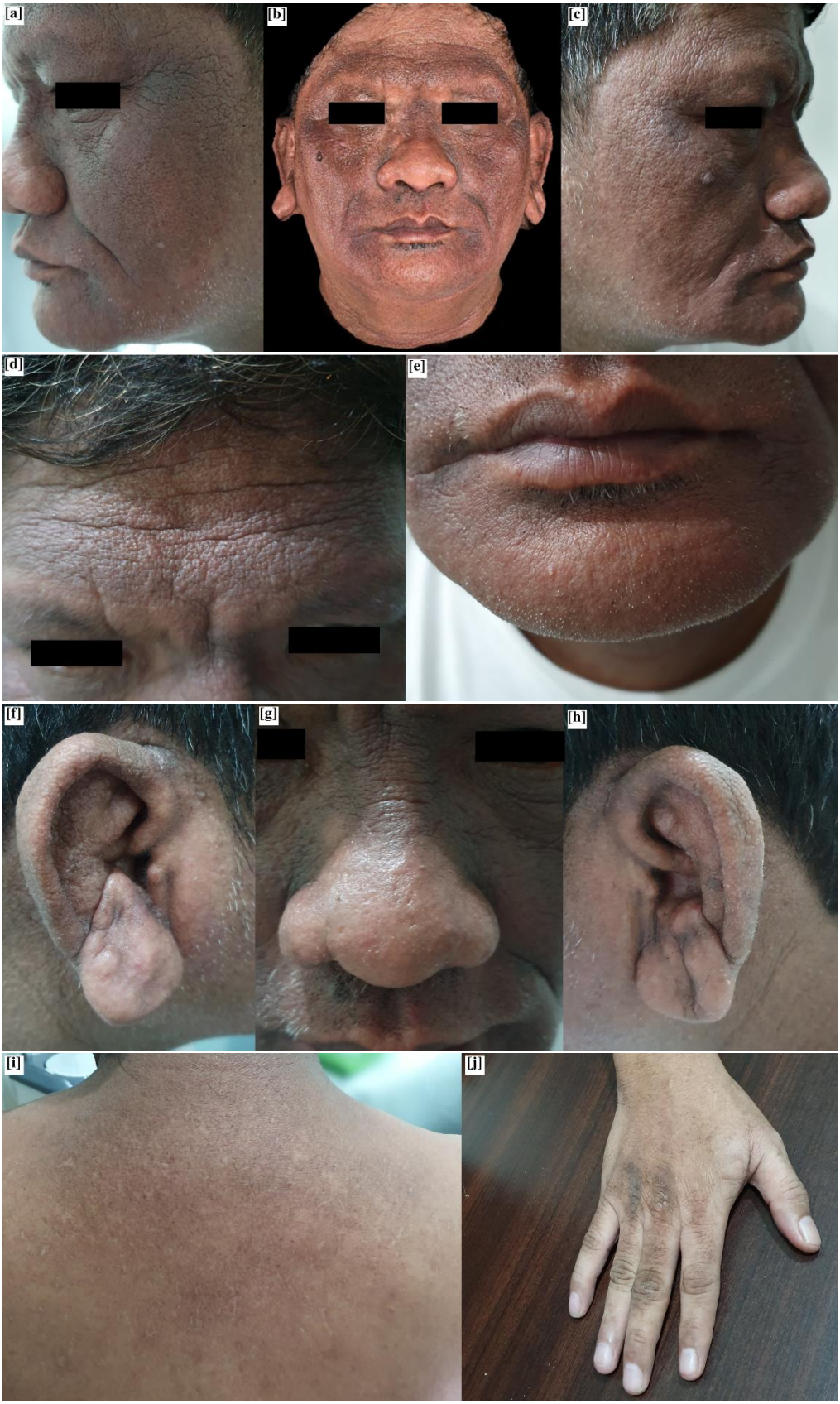

Figure 1: Hyperpigmented velvety thickening of the skin on the left cheek (a), face (b), right cheek (c), forehead (d), chin (e), neck (i) and knuckles (j). Rhinophyma (g) and otophyma (f,h) were also observed.

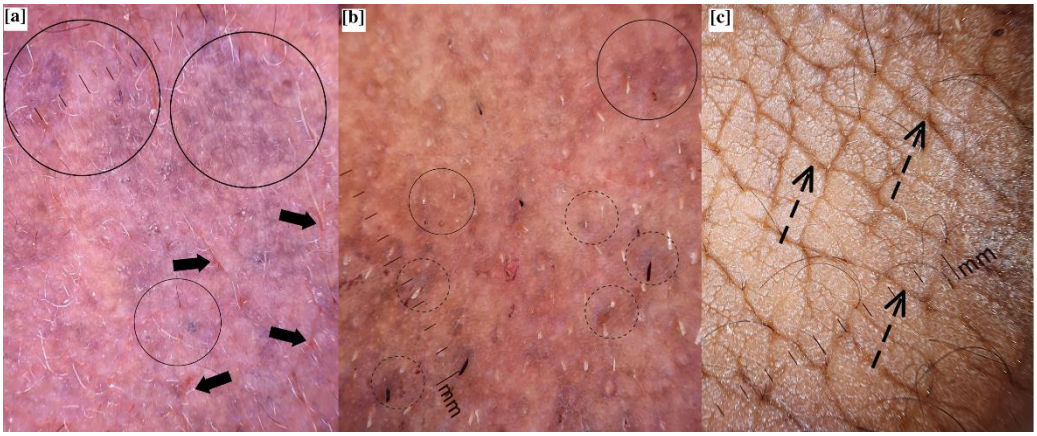

Figure 2: Dermoscopy of the cheeks demonstrated bluish gray areas (black circle) with telangiectasias (black arrow) (a) Dermoscopy of the chin bluish gray areas (black circle) and thickened perifollicular hyperpigmentation (dotted circle) (b) Dermoscopy of the nape revealed markedly depressed sulci (dotted arrow) (c) ((a-c. Dermlite DL2x10)

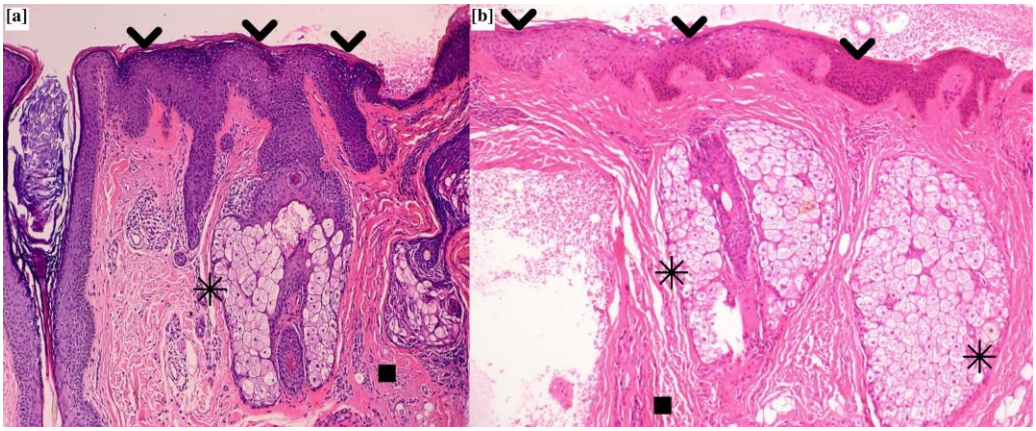

Figure 3: Histological examination of the cheek revealed parakeratosis of the stratum corneum. There is acanthosis of the epidermis, hypergranulosis (arrowheads) and mild spongiosis. The dermis reveals prominent fibrosis (black box) and enlarged sebaceous lobules (asterisk). Fibrosis is also seen in the lower dermis (black box) (a) Another biopsy on the left earlobe revealed mild acanthosis of the epidermis with basal cell layer hyperpigmentation (arrowheads). The dermis reveals fibrosis (black box) and enlarged sebaceous lobules (asterisk). Fibrosis is seen in the lower dermis (black box) (b) (a&b. H&E, 100x). The 2 biopsies are consistent with acanthosis nigricans and phymatous rosacea.

Discussion

Acanthosis nigricans clinically presents as hyperpigmented coarse thickened velvety plaques involving the intertriginous areas and, in our case, the face. Insulin has been demonstrated to cross the dermoepidermal junction and the binding of insulin to insulin-like growth factor 1 receptors stimulates proliferation of keratinocytes and fibroblasts leading to formation of AN. Hyperinsulinemia indirectly causes AN by increasing circulation of free IGF-1 levels. The increase of plasma concentration promotes cell growth and differentiation [4].

A clinico-investigative study of facial AN was done by Shah et al.[5] which investigated forty cases of facial AN and forty cases of healthy non-obese individuals. In their study, their clinic-dermoscopic-histological correlation showed that lighter brown variants of facial AN had follicular plugging and subtle sulci pattern accompanied by irregular brown globules and perifollicular pigmentation on dermoscopy and mild hyperkeratosis and basal cell layer hyperpigmentation with minimal

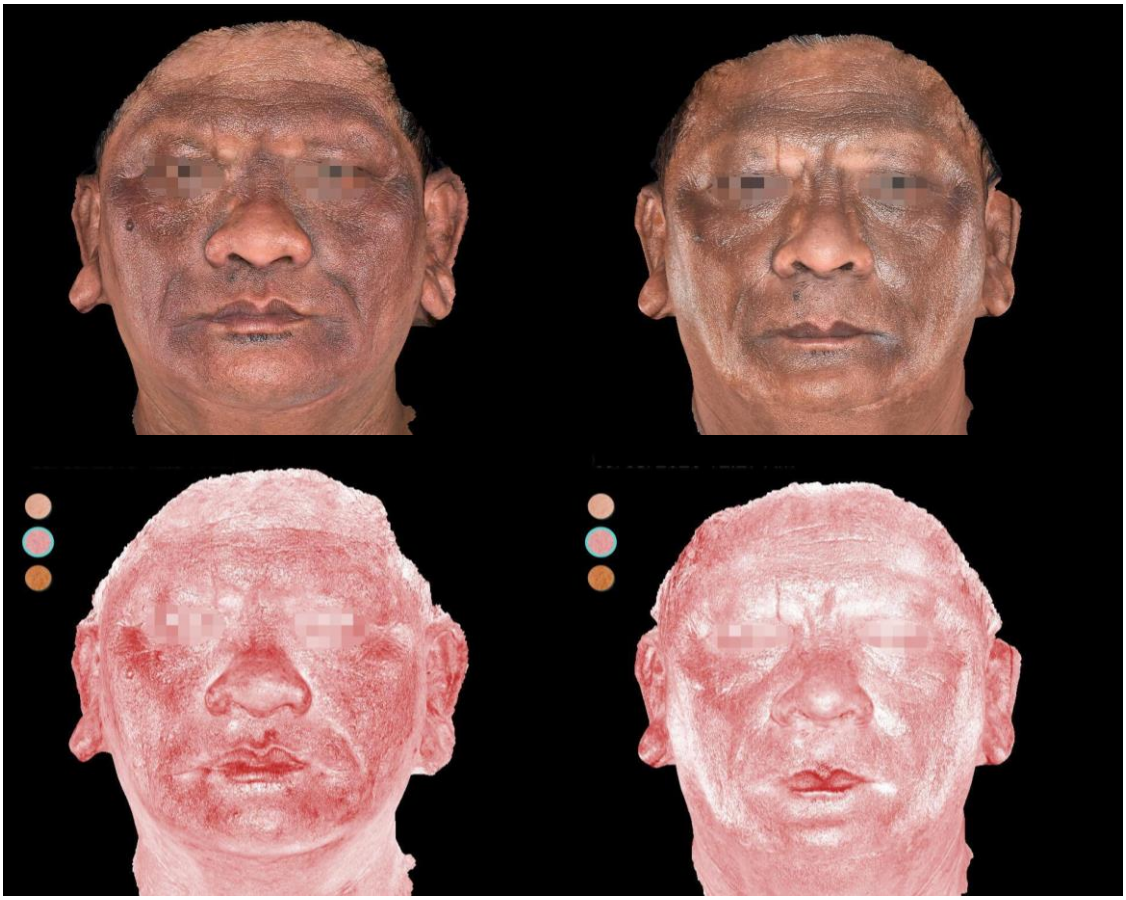

Figure 4: Decreased of phyma, hyperpigmentation and redness after three months of topical and oral medications with every 2 weeks session of pro-yellow laser 577nm.

acanthosis and papillomatosis on histopathology. On the other hand, dark-brown to black facial AN (chronic variants) showed prominent sulci, bigger brown globules, and perifollicular hyperpigmentation on dermoscopy and moderate hyperkeratosis and hypermelanization of the basal layer with moderate to severe acanthosis and papillomatosis on histopathology [5]. Our dermoscopy and histopathology findings of epidermal acanthosis, papillomatosis and hyperekeratosis were similar to the study of Shah et al. and Hermanns et al.7 where they found out that AN occur due to the acanthosis, papillomatosis, and hyperkeratosis of the epidermis. The hyperpigmentation seen in AN may be attributed to the activation of insulin-like growth factor-1 receptors (IGF-1) on the keratinocytes leading to its proliferation resulting to hyperkeratotic plaques clinically appearing as velvety hyperpigmented plaques [6,7].

The strong association between rosacea and metabolic disorder has already been established in previous studies. In a case-control study among 47 age-, gender-, and body mass indexed (BMI)-matched rosacea patients and 50 healthy controls, the rate of insulin resistance was significantly higher in rosacea group versus control suggesting a positive correlation between the two conditions [8]. Aside from this significant positive correlation with insulin resistance, cardiovascular disease risk factors, such as fasting blood glucose, lower density lipoprotein, total cholesterol, triglyceride, and systolic blood pressure and diastolic blood pressure levels, were significantly higher in patients with rosacea compared with the control group. Furthermore, results from a multi-institutional case-control study among systemic comorbidities in Korean

patients, Woo et al.[10] found a strong correlation between rosacea and metabolic syndrome (diabetes melitus, obesity and dyslipidemia). Casas et al.[9] analyzed the skin of rosacea patients and found higher expression of genes encoding pro-inflammatory cytokines (Il-8, Il-1b, TNF-a) and inflammasome-related genes (NALP-3 and CASP-1). In addition to their study, elevated levels of LL-37, VEGF, CD45RO, MPO, and CD163 were also found indicating widespread activation of the immune system [9,10]. Clinical findings in our patient include phyma, transient facial erythema and symptoms of burning, erythema, edema and dryness. Although patient complains of persistent warmth, skin redness cannot be thoroughly evaluated because of his dark skin phototype. While it is evident that the presence of erythema and telangiectasia are difficult to identify in patients with skin of color, having great awareness on other clinical signs such appearance of xerosis, scales, edema, acneiform papules and pustules is essential for the correct diagnosis and management.

Both the pathogenesis of rosacea and diabetes involves systemic inflammatory factors. While the relationship between rosacea and diabetes has not been fully elucidated yet, oxidative stress and systemic inflammation are hypothesized to contribute to the development of rosacea, insulin resistance, and complications associated with diabetes. In a study by Hua et al.[11], systemic inflammation associated with rosacea leads to structural alterations in lipoproteins, resulting in derangement in lipid profile contributing to the metabolic syndrome [11]. In addition to the systemic inflammation caused by rosacea, numerous inflammatory skin conditions have oxidative stress as their underlying cause and has been suggested to be involved in the pathophysiology in rosacea. In a case-control study by Karabay et al.[12], the group were compared with the total antioxidant status (TAC) and total oxidant status (TOC) between healthy controls and patients with rosacea. It was found that patient with rosacea have increase of oxidative stress level which manifested through higher levels of TOC [12]. Paraoxonase-1 (PON1) is an antioxidant enzyme associated with high-density lipoprotein (HDL) and plays a crucial role in the protection against atherosclerosis through serum lipoproteins oxidative modification and lipid peroxides hydrolysis. PON has demonstrated its activity in reducing the risk of metabolic syndrome, atherosclerosis, and diabetes mellitus and was found to be decreased in patients with rosacea [13].

To address the normalization of epithelial growth and differentiation, the patient was prescribed with an oral retinoid such as isotretinoin. A 33-year-old woman who had extensive AN including the axillae, groins, antecubital fossae, dorsa of the hands, angles of the mouth and areas under the breasts was treated with oral isotretinoin in a case report by Katz[14]. In the study, the patient began a regimen of 0.5mg/kg/day and was eventually increased to 1.5mg/kg/day with flattening and lightening of color on the lesions on the neck with other areas unchanged. Three weeks later, the dosage was increased to 3mg/kg/day, with flattening and returning of normal skin color. However, side effects such as severe cheilitis and dose-related elevation of serum triglyceride levels were observed prompting to decrease the dosage to 2mg/kg/day. After 16 weeks, the drug was discontinued with the darkening and thickening of the lesions recurring. The patient was eventually maintained at a dosage of 2mg/kg/day with good clinical response and minimal side effects [14]. In our study, patient was prescribed a low-dose oral isotretinoin due to the concomitant co-morbidities and the surface area involved.

Currently, there is no superior treatment for AN. However, treatment modalities such as topical tretinoin, topical vitamin D analogs, chemical peels and other tyrosinase inhibitors. Chemical peels, oral retinoids and use of 755 nm lasers may provide

benefit in some studies (15). Surgery and ablative laser treatment were recommended for local treatment of phymatous rosacea in the four guidelines/consensus, and isotretinoin was recommended for systemic drug use. The Global Rosacea treatment guidelines and expert require oral doxycycline or isotretinoin in cases of inflammatory type of phymatous rosacea. In severe cases, CO2, Erbium:yag laser or surgical excision and resection may provide therapeutic effects [16].

Conclusion

It can be challenging to describe AN and rosacea in individuals with skin of color. Increase awareness of both entities might aid in the timely diagnosis and effective treatment of this condition. Clinical presentation, dermoscopy and histopathology still remains to be the gold standard in the diagnosis. While cosmetic resolution is recommended for patients with this condition to improve their quality of life, healthcare professionals should first and foremost make an effort to identify and manage any potential underlying conditions, such as metabolic syndrome, diabetes mellitus and cancer.

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