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EDITORS WELCOME

Dear Canadian Dermatology Community,

Welcome to our final issue of *Canadian Dermatology Today* in 2021! Despite a difficult year in the face of the ongoing COVID-19 pandemic, the country has achieved greater than 80% full vaccination rates for patients aged 5 and up which is a remarkable accomplishment. Our hope for all our colleagues and their families is continued good health in 2022!

In this final issue of the year we are pleased to share content with you that focuses on non-invasive diagnostic technologies for melanoma, the role of artificial intelligence in dermatology and an update on non-invasive techniques for skin tightening. Additionally, we have two wonderful articles on onychomycosis and prurigo nodularis that we are sure our readers will enjoy.

As always, we hope you find these articles informative and helpful. We are grateful for your continued readership, and we look forward to another great year in 2022. We are also immensely grateful for the continued support of our sponsors who have demonstrated a commitment to credible and relevant medical education through their support of this journal.

Please let us know how we are doing by suggesting topics and feel free to share our registration link at canadiandermatologytoday.com with your peers so that, they too, can subscribe to future issues!

Finally, as this year draws to a close, we wish you and your families a wonderful and peaceful holiday season.

Best wishes,

Kim Papp, MD Jensen Yeung, MD Melinda Gooderham, MD Chih-ho Hong, MD

TABLE OF CONTENTS

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Dr. Michael Copley is a medical dermatologist with dual board-certification in Canada and the United States. He also holds a PhD in Experimental Medicine from the University of British Columbia (UBC) and maintains a keen interest in both clinical and basic research. As a clinical instructor within UBC's Department of Dermatology and Skin Science, he is passionate about both undergraduate and graduate level dermatology education. His clinical interests include skin cancer, autoimmune diseases of the skin and telemedicine.

NON-INVASIVE DIAGNOSTIC TECHNOLOGIES FOR MELANOMA

Clinical examination followed by excisional biopsy and histopathologic analysis of suspicious pigmented lesions remains the gold-standard for melanoma diagnosis. Unfortunately, the performance of the unaided "melanoma detection pathway" is far from optimal with dermatologists demonstrating only 63.6% sensitivity[1] and primary care physicians only 40.2% sensitivity for correct melanoma identification[2] in a community-based screening setting. The accuracy of unaided melanoma detection is also low with a number needed to excise (NNE), defined as the number of suspicious lesions that must be excised to detect a single melanoma, of 29.4 for non-specialists and 8.7 for specialists.[3] In order to improve melanoma detection, new non-invasive techniques have emerged including dermoscopy, total body photography, reflectance confocal microscopy and the pigmented lesion assay, which have a potential capacity to improve melanoma diagnosis. Such techniques used either alone, in combination, or with computational approaches including artificial intelligence (AI), have the potential to revolutionize the melanoma detection pathway for the benefit of patients and clinicians alike. Some of these technologies also provide an alternative to surgical biopsy in cases where patients decline such a procedure or to aid in the decision of whether to proceed with surgical biopsy when the clinical findings are equivocal. Such techniques also have application in the assessment and monitoring of high-risk patients including those with a history of melanoma, with multiple atypical nevi or with melanoma predisposition syndromes. They may also improve triage of referrals from non-specialists and help reduce healthcare costs by decreasing unnecessary surgical biopsies. In this review, the key features of established and emerging visual and non-visual non-invasive melanoma diagnostic technologies are highlighted.

Visual Techniques: Dermoscopy, Sequential Digital Dermoscopic Imaging and Total Body Photography

Dermoscopy

Of all technological advances aimed at increasing the sensitivity and specificity of melanoma detection, dermoscopy has arguably had the most substantive impact. While the technique dates back more than 100 years, it was not until the publication of a seminal paper by Pehamberger et al. in 1987 that a formalized approach to the interpretation of dermoscopic findings of pigmented lesions, termed "pattern analysis", was established.[4] This study was followed soon after by descriptions of algorithmic approaches to pigmented lesion dermoscopy including the ABCD rule for dermoscopy[5], the 7-point checklist[6], the Menzies rule[7], the CASH

algorithm[8] and the chaos and clues method.[9] In a study comparing the validity and reliability of such criteria when used by dermatologists, general practitioners, medical students and residents, sensitivity for melanoma detection was found to be between 70 and 95%; however, all methods showed poor interobserver agreement.[10] Additionally, many dermatologists likely do not employ any of these algorithms and instead rely on pattern analysis which has been defined as "the simultaneous assessment of the diagnostic value of all dermoscopy features shown by the lesion", an approach which has been shown in one study to have a higher diagnostic accuracy than the ABCD rule and the 7-point checklist.[11] Regardless of the method used for interpretation, there is now an overwhelming body of evidence, including four meta-analyses[12-15], for improvement of melanoma detection through the routine use of dermoscopy.

Sequential Digital Dermoscopic Imaging

Although clinical appearance with the addition of dermoscopy can provide important static information about a pigmented lesion's probability of being classified as melanoma, dermatologists rely on subjective patient history to gain knowledge of dynamic features suggestive of melanoma including lesional change or symptoms. Sequential digital dermoscopic imaging (SDDI) represents a variation of classical dermoscopy which permits objective assessment of lesional evolution. This is accomplished by obtaining baseline digital dermoscopic images and follow-up images and comparing these images for change in size, colour or structure/pattern[16] (**Table 1**). For patients at high-risk for melanoma including those with the familial typical mole and multiple melanoma syndrome or atypical mole syndrome, the use of SDDI has been shown to increase melanoma detection 2-fold compared to the use of the 7-point checklist alone.[17] Additionally, melanomas detected by SDDI are significantly thinner at the time of diagnosis.[17] In low-risk patient groups, however, the addition of SDDI appears to be of limited additional value[18,19] and may in fact lead to false positives.[20] One of the reasons for this, particularly in younger patients, may be that growth represents a normal biologic feature of benign nevi and thus the interpretation of any changes noted with this technique requires careful interpretation to distinguish an expected change of benign nevi from a pathologic feature of melanoma. Features that should prompt excision include (1) architectural changes, (2) asymmetric increase in size, (3) new colors, depigmentation and focal colour changes and (4) the appearance of a melanoma criteria such as black dots or regression (**Table 1**).[21] Limitations of this technique include the possibility of decreased sensitivity if a patient does not return for their follow-up visit, the requirement for digital storage and organization of photos and the additional time required for image comparison. Despite these limitations, SDDI appears to be an effective strategy for improvement in sensitivity as compared to dermoscopy for detecting melanoma which is particularly valuable in high-risk patient populations.

Total Body Photography

Another technique aimed at increasing detection of melanoma in patients with numerous nevi is total body photography (TBP). Advantages of this technique over SDDI are its ability to detect de novo melanomas or melanomas arising within benign appearing nevi not otherwise selected for monitoring.[22] In a study of U.S. academic dermatologists in 2010, 71% of respondents reported regular use of TBP[23]; however, this is likely much lower in the community setting.

In a recent 5-year cohort study of melanoma patients, 48.1% of second primary melanomas were detected using TBP with a number needed to excise of 1:1.3.[24] It has also been associated with a reduction in biopsies and a lower NNE[25,26] in some studies but no difference in biopsy rates in others.[27] Part of the reason for such discrepancies might be the rapidly changing technology available to both acquire and interpret TBP images with the most advancements being automated and 3-dimensional TBP.[27] Limitations of this technique include the significant cost of equipment, the

Interval Change	Nevus	Melanoma
Size	No growth Symmetrical growth	Asymmetric growth
Colour	No change Even lighter/darker brown Even lighter/darker erythema	New colours, especially focally Depigmentation
Structure	No change Subtle changes including accentuation of existing structures	Architectural changes Appearance of new structures including classical melanoma criteria and regression

Table 1. *Differentiating features of nevus and melanoma in follow-up images (Adapted from Tschandl et al.)[21]*

need for a dedicated space and personnel, and the time required for image acquisition and analysis. An added benefit of TBP is the decrease in cancer worry.[28]

Non-Visual Techniques: Reflectance Confocal Microscopy and Pigmented Lesion Assay

Reflectance Confocal Microscopy

Reflectance confocal microscopy (RCM) is a technique which allows for imaging to a depth of the upper papillary dermis (a depth of 200 μm) with a near-infrared laser (830 nm).[29] In a recent meta-analysis, RCM was found to have a pooled sensitivity of 92.7% and specificity of 78.3% for melanoma detection.[29] Additionally, in a prospective study of RCM in combination with dermoscopy, the addition of RCM decreased the NNE from 14.6 to 6.8.[30] When compared to dermoscopy, it is superior for recognition of in situ melanoma and diagnosis of amelanotic lesions and mucosal lesions; however, it cannot be used on acral skin.[29] Its widespread use is also limited by the significant cost of purchase and maintenance as well as the substantial training required to gain proficiency.

Pigmented Lesion Assay

The pigmented lesion assay (PLA) is a proprietary test developed by DermTech, Inc. (La Jolla, CA) which is designed to aid in deciding whether to proceed with surgical biopsy of pigmented lesions. Its use involves harvesting cells from the stratum corneum overlying a pigmented lesion in question using a non-invasive "tape stripping" method, followed by the measurement of transcript levels of two genes that are expressed predominantly by melanoma as compared to benign pigmented lesions (LINC00518 and PRAME). While the validation and registry studies for the PLA showed a 91-95% sensitivity and 53-91% specificity for melanoma detection with an estimated negative predictive value (NPV) of 99%[31,32], several follow-up analyses have been critical of the prevalence rates used to calculate this NPV and propose less impressive performance metrics in the real-world setting.[10,33] Further studies are required to establish the role of the PLA in the melanoma detection

Technology	Description	Advantages	Cost	Disadvantages and Limitations
Dermoscopy	Direct examination of pigmented lesions with polarized/non-polarized magnification	Well-validated Efficient and convenient for both patient and provider	$	Requires significant training/experience to gain proficiency Time consuming if many lesions
SDDI	Longitudinal dermosocpic re-imaging of individual lesions	Good evidence for increasing melanoma detection in high-risk populations Minimal additional equipment required	$$	Limited by patient compliance Lengthy time for acquisition/ comparison Digital storage required
TBP	Clinical imaging of entire skin surface Automated TBP machines available from Canfield Scientific (Parsippany, NJ), DermSpectra (Tucson, AZ), Fotofinder (Columbia, MD) and Melanoscan (Stamford, CT)	Allows for identification of new and changing lesions Image acquisition does not need to be done by dermatologist	$$$	Most units require dedicated space Referencing TBP images may lengthen time of office visit
RCM	In vivo near histology-grade imaging to level of papillary dermis	Can be used on amelanotic, facial or mucosal lesions Helpful for presurgical mapping	$$$	Image capture takes up to 5 minutes per lesion Cannot be used on acral skin Significant training/ experience required for image interpretation
PLA	Diagnostic test involving "tape stripping" followed by measurement of LINC00518 and PRAME	Rapid procedure (<5 min) Useful for cosmetically sensitive areas or as alternative for patients that decline surgical biopsy Rapid turnaround time High negative predictive value	$$	Controversy remains whether sensitivity and specificity are sufficiently high Cannot be used on acral or mucosal surfaces

Table 2. *Comparisons of non-invasive melanoma diagnostic technologies (Adapted from Fried et al.[34,35])*
SDDI, serial digital dermoscopic imaging; TBP, total body photography; RCM, reflectance confocal microscopy; PLA, pigmented lesion assay

pathway; nevertheless, it provides a promising proof-of-concept for in vivo molecular diagnostics for melanoma.

Conclusion and Future Directions

Melanoma remains a challenge for even the most experienced dermatologist with significant clinical consequences for a delayed or missed diagnosis. As clinicians, we must be judicious with the employment of any new diagnostic technique, particularly those that carry significant financial costs or potential for harm, but also open to their use if they can improve diagnostic accuracy thereby leading to earlier detection and treatment. The non-invasive techniques described herein, along with new and emerging techniques including high-frequency ultrasound, optical coherence tomography and electric impedance spectroscopy, have the potential to improve the efficiency and efficacy of the melanoma detection pathway for the benefit of both dermatologists and their patients (**Table 2**). Nonetheless, clinicians must remain vigilant of "technological creep" and only adopt such techniques when there is ample comfort with their evidence and risk-benefit ratio.

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APPROACH TO DIAGNOSIS AND MANAGEMENT OF REACTIVE INFECTIOUS MUCOSAL ERUPTION (RIME)

Background

Mycoplasma pneumoniae (MP) induced rash and mucositis (MIRM), also known as reactive infectious mucosal eruption (RIME), was first described as a distinct entity in 2015.[1] This condition has historically been under the diagnostic umbrella of erythema multiforme, and within the spectrum of Steven's Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). RIME/MIRM is, however, a separate entity with distinct clinical features requiring a specific approach to providing accurate diagnosis, treatment and optimize patient outcomes.

Mycoplasma pneumoniae is a bacterial infection that is a common cause of community acquired pneumonia in children over 5 years of age and adolescents.[2,3] In addition to respiratory findings, MP is also known to have a number of extra-pulmonary manifestations and has been identified as a cause of significant mucositis and cutaneous rash in the pediatric population and less commonly in adults.[4] Other infectious triggers have also been identified in cases of RIME and include *Chlamydophila pneumonia*, Influenza B, and a number of other respiratory viruses.

Clinical Presentation

A systematic review by Canavan et al. (2015) noted the average age of patients presenting with RIME/MIRM was 11.9 +/- 8.8 years and the majority were male (66%). As well, prodromal symptoms such as cough, fever and malaise were seen in almost all patients and typically presented one week before the onset of the cutaneous eruption.[1] Mucosal involvement is seen in almost all patients with suspected RIME/MIRM. The oral mucosa is most often involved (94% of patients), followed by the ocular mucosa (82% of patients), and urogenital mucosa (63% of patients).[1] Oral mucosal lesions include erosions, ulcers, vesiculobullous lesions and erosive sloughing of the entire buccal mucosa. Ocular lesions were found to include purulent bilateral

conjunctivitis, photophobia and eyelid edema. The urogenital mucosa was noted to include lesions that were vesiculobullous as well as erosions and ulcerations of the meatus, penile shaft, scrotum, vulva and vagina.[1]

Skin lesions in RIME/MIRM patients are polymorphic. In the review by Canavan et al., the authors found that vesiculobullous lesions were most frequently seen (77% of patients), followed by targetoid lesions (48% of patients), papules (14% of patients), macules (12% of patients) and a morbilliform eruption (9% of patients).[1] In contrast to those presenting with SJS, cutaneous lesions in RIME/MIRM are generally sparser with only a few scattered lesions. The most common distribution was acral (46% of cases), followed by generalized (31% of cases) and truncal (23% of cases).[1] This is another differentiating feature from SJS. Typically, SJS skin lesions will begin centrally on the trunk and spread distally with progression of the disease.

Diagnosis of RIME/MIRM

Clinical suspicion for RIME/MIRM should be high in pediatric patients presenting with a prodrome of cough, fever and malaise along with mucosal erosions and ulcerations and sparse acral skin lesions. Depending on clinical presentation, baseline blood work may be indicated. This could include routine blood tests (such as complete blood count, liver and renal function and inflammatory markers such as ESR or CRP) but other tests may be required depending on clinical presentation and therapeutic considerations.[4] Nasopharyngeal or oropharyngeal swabs for *Mycoplasma pneumoniae, Chlamydophila pneumoniae* and respiratory viruses should be performed. Polymerase chain reaction (PCR) testing is generally preferred for these swabs given the rapid turnaround time as well as the test's high sensitivity and specificity.[4] Consideration can be given to a chest x-ray as well but radiographic findings of *Mycoplasma pneumoniae* infection can be variable and can resemble findings seen in children with other viral respiratory infections. Focal reticulonodular opacities confined to one lobe is typically the most common finding in *Mycoplasma* pneumonia.[5] Punch biopsy of the skin can be performed to help rule out other conditions that may be on the differential diagnosis such as pemphigus vulgaris, but histologic findings in MIRM/RIME would be similar to SJS and TEN and would most likely not aide in differentiating between drug or infectious triggered epidermal necrolysis.

Diagnosis of RIME
Consider RIME in patients with cough, fever, malaise and erosive mucosal disease with sparse cutaneous involvement
Oral mucosa is most often involved followed by ocular and genital mucosa, respectively
Lesion morphology and absence of medication exposure helps differentiate from erythema multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis

Management of RIME/MIRM

Given the extent of mucosal involvement, many patients with RIME/MIRM require admission for pain management and nutritional support, in addition to treatments directed at the underlying condition. A recent review by Dr. Michele Ramien contains a comprehensive approach to managing patients with RIME/MIRM and includes a broad overview containing the following recommendations listed below.[4]

Upon diagnosis of RIME/MIRM, patients should be assessed as to whether they require admission to hospital. Generally, these patients can be managed on a pediatric medical unit but may need contact and droplet precautions if *Mycoplasma pneumoniae* is suspected. These patients should receive supportive care including a bland, soft food diet along with pain control, which may include acetaminophen, NSAIDs and occasionally opioids. Cases with significant mucosal involvement should also be consulted to appropriate services such as ophthalmology, urology or gynecology to avoid potential long-term complications such as mucosal synechiae.[1]

Workup of RIME
Test for respiratory infections including *Mycoplasma pneumoniae* in patients with suspected RIME
PCR testing is preferred given rapid turn-around and high sensitivity and specificity
Consider chest x-ray in patients with suspected *Mycoplasma pneumoniae* infection

Medical therapies aimed at treating mucosal lesions may include "magic mouthwash" (a compounded rinse with ingredients such as analgesics, anti-inflammatories and antimicrobials), chlorhexidine rinses or topical corticosteroids such as clobetasol for oral and urogenital lesions. In patients with ocular involvement, topical therapies such as artificial tears, dexamethasone or antimicrobial eyedrops (such as moxifloxacin) can be initiated.[4]

Therapies directed at the infectious trigger, typically *Mycoplasma pneumoniae*, should also be initiated promptly if there is suspicion of underlying infection. First line treatment for MP includes macrolide antibiotics such as azithromycin. Other possible antimicrobial options include tetracyclines or fluroquinolones. Doxycycline is typically avoided in patients less than 8 years of age due to the potential for tooth discoloration, but this is considered to be a low-risk adverse event with short-term use.[6] Typical treatment duration varies by antibiotic but is usually 5 days for azithromycin, with usual dosing, and 7-10 days for alternatives.

There are currently no guidelines regarding treatment of active RIME/MIRM as there have been few studies published on optimal management of this condition. Treatment has historically been similar to the treatment of SJS/TEN. Therapies that have been used include systemic corticosteroids, intravenous immunoglobulin (IVIG), cyclosporine and anti-TNF biologic agents such as etanercept or infliximab. According to previous studies, systemic corticosteroids have been used in approximately 31% of cases and IVIG in 9% of cases.[1,7] Corticosteroids have been shown to not only treat the inflammation associated with RIME/MIRM, but also to provide benefit at treating the underlying pneumonia.[8] A case series by Li et al. (2019) showed that early initiation of cyclosporine may reduce duration of hospital admission to 5-7 days compared to approximately 14 days in patients treated with systemic corticosteroids and IVIG. Dosing of cyclosporine in these cases was 3-5mg/kg/day and was given on average for 7-10 days in total.[4,9]

Treatment of RIME
Many patients with RIME require admission for pain control and nutritional support
Treat for *Mycoplasma pneumoniae* if there is suspicion of underlying infection
Corticosteroids, cyclosporine, IVIG, and anti-TNFα agents have been used to treat RIME with variable success

Prognosis of RIME/MIRM

In general, most patients recover completely with no long-term sequelae.[1] Recurrences of RIME/MIRM are infrequent but are estimated to occur in 8-38% of cases.[1,10] A recent publication by Liakos et al. noted that recurrences of RIME/MIRM tended to be less severe with regards to both skin and mucosal findings, which corresponded to lower rate of admission to hospital or shorter duration of hospital stay.[10] Ocular mucosal synechiae and mucocutaneous dyschromia are the most commonly observed complication. Severe complications, similar to those seen in SJS/TEN, are very rare. As well, in contrast to SJS/TEN, mortality is much lower and estimated at 3%, but these numbers may be an overestimate as this was observed in studies published prior to widespread use of antibiotics for *Mycoplasma pneumoniae*.[1]

Conclusion

Reactive infectious mucosal eruption in the pediatric population is characterized by a prodrome of cough, fever and malaise followed by erosive mucosal disease and polymorphic cutaneous lesions. Mucosal involvement can be severe and hospitalization is frequently needed for nutritional support and pain control. Patients should be screened for *Mycoplasma pneumoniae* infection by PCR testing of nasopharyngeal or oropharyngeal swabs, and therapies directed at mucosal and skin care should be initiated. In some cases, systemic medications such as cyclosporine, corticosteroids or IVIG can be used. Specifically, cyclosporine has shown promising results at reducing duration of disease and length of admission in hospital.

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SKIPPING THE SCALPEL: UPDATES ON NON-INVASIVE SKIN TIGHTENING

Introduction

The cosmetic consult is often the initial step in a patient's positive aging journey. It is a moment where the patient may feel at their most vulnerable, stripped of the usual makeup they might use to make themselves feel better, or commonly, to hide perceived imperfections. The patient may be excited, nervous, or hopeful that in your hands their aesthetic goals will be reached. Patients may arrive informed, they may have "no idea where to start" or may want the "same thing" that a friend of a friend achieved under your care. It is the physician's expertise that will guide both the discussion and the recommendations that are made. The initial consult helps to establish patient goals and expectations and is a foundation for a successful treatment plan. Observing the patient as they discuss their area(s) of concern is often accompanied by their self-analysis in the mirror, words they associate with how they feel, or occasionally, to the exact physical goals they hope to achieve. "I just wish I could get a little lift", the patient might say as they pull along their zygomatic arch and jawline. It comes as no surprise to experienced clinicians that discussions around the concepts of "lifting" and "tightening" frequently permeate the cosmetic consultation.

Discovering effective methods of non-invasive and minimally invasive correction of skin laxity have long been elusive goals of aesthetic medicine, with patient demand for such services increasing over 600% in the past 15 years.[1] Providing solutions to patients with minimal downtime, while still delivering impactful results, is often a challenge given the multifactorial nature of laxity. While metabolic and behavioural factors such as age, smoking and weight loss may contribute, the biology of skin laxity is a complex process. Decreasing skin elasticity, bone resorption, muscle atrophy and connective tissue changes all lead to the dreaded "sag". Is skin tightening without a scalpel still a myth, or is it now a reality?

The following review will outline selected in-office treatments with the primary objective to improve skin laxity, and to tighten or firm the patient's skin. Readers should note that many dermatologic procedures and devices can indirectly contribute to skin tightening, however this article will focus on those with this outcome as their primary treatment objective (**Table 1**).

Injectables
Hyaluronic Acid
Calcium Hydroxylapatite
Poly-L-Lactic Acid
Devices
Microfocused Ultrasound with Visualization (Ultherapy®)
Non-Invasive Radiofrequency (Thermage®, INFINI®, Profound® RF, Exilis®, Morpheus8®)

Table 1. *Select Non and Minimally Invasive Modalities for Skin Laxity Improvement; courtesy of Brittany Waller, MD*

Hyaluronic Acid Fillers

Addressing volume deficiencies with hyaluronic acid (HA) can improve not only the treatment area, but also have a positive impact elsewhere, as volume loss and facial proportions become more balanced. The satisfaction of filling the mid face and noticing improvement in tear troughs, nasolabial folds, marionette region or jawline is rewarding for both patient and injector alike.

While traditionally used to volumize or restore structure lost as part of the aging process, the injection of microaliquots of HA into large areas of the dermis has recently been shown to induce neocollagenesis and enhance skin turgor and firmness.[2] The hydrophilic nature of HA also contributes to positive effects in skin elasticity, hydration and structure.[2] A more brighter and smooth surface appearance can be achieved after a series of treatments.[2] The most common adverse events while using a microaliquot HA injection technique include bruising and edema but are generally minimal and well tolerated.

Calcium Hydroxylapatite

Calcium hydroxylapatite microspheres (CaHA, Radiesse®; Merz Pharmaceuticals GmbH, Frankfurt, Germany) comprise biodegradable particles in an aqueous carboxylmethyl cellulose gel carrier.[3] After injection, the particles induce histiocytic and fibroblastic response, acting as a scaffold for new tissue formation and stimulate collagen and elastin production around the implant for sustained aesthetic improvement.[4]

CaHA is approved to correct moderate-to-severe folds/wrinkles and to address soft-tissue volume loss in the face and hands.[5] More recently, subdermal injection using dilute CaHA has been found to improve skin laxity without creating a volumizing effect.[4] CaHA, a highly viscoelastic product, is typically suited for supraperiosteal, subdermal and deep-dermal placement but can be injected superficially for dermal rejuvenation when hyperdiluted.[6] When given as a subdermal wash across the treatment area, hyperdiluted CaHA is felt to be more biostimulatory than the undiluted form. Hyperdiluted CaHA encourages targeted neocollagenesis in the injection area to improve laxity and overall skin quality in the mid- and lower face, neck, decolletage, upper arms, abdomen, upper legs and buttocks. Dilution ratios of at least 1:1 for pan facial rejuvenation and 1:2-1:6 for neck, decolletage and body are often reported in the literature.[4]

Treatments are often used as an adjunct to volume augmentation or combined with additional modalities such as energy-based devices for optimal results. Adverse events include bruising, swelling, pain and induration. In thinner and darker skin types, too-superficial product placement may lead to additional adverse events such as product visibility and hyperpigmentation.[7]

Poly-L-Lactic Acid

Poly-L-lactic acid (PLLA) is a biodegradable, biocompatible, synthetic polymer from the alpha-hydroxy-acid family.[8] PLLA was initially approved by the FDA in 2004 for the treatment of facial lipoatrophy associated with human immunodeficiency virus, with approval for cosmetic indications in immunocompetent patients achieved in 2009.[8] Sculptra® (Dermik Laboratories, Bridgewater, NJ) is a commercially available injectable implant that contains microparticles of PLLA in a carboxymethylcellulose and mannitol powder. After reconstitution, Sculptra® is injected into the reticular dermis/subcutaneous plane, stimulating the production of fibroblasts, subsequently leading to collagen production and gradual increase in facial volume after a series of treatments.[9]

The collagen boosting response of hyperdiluted PLLA has also been explored off-label in the neck, chest and body for rejuvenation. Similar to CaHA, when hyperdiluted, the effects of PLLA are thought to be more biostimulatory than volumizing in nature.[10] Even distribution of the product is of utmost importance for minimizing the appearance of papules, nodules and granuloma formation. Most adverse events are mild, including bruising, erythema and edema which typically resolves in a matter of days.[9]

Microfocused Ultrasound with Visualization

Microfocused ultrasound with visualization (MFU-V) (Ultherapy®, Ulthera Inc, Mesa, AZ) is a Health Canada approved treatment for non-invasive eyebrow, submental and neck lift as well as for improvement in lines and wrinkles on the décolleté.[11] Ultrasound imaging is incorporated as part of the treatment protocol to visualize treatment target and to assess proper coupling of the transducer to the skin.[12]

MFU-V is designed to produce microthermal zones of coagulation in the mid-to-deep reticular dermis and sub-dermal fibromuscular layers including the superficial musculoaponeurotic system (SMAS).[12] A wound-healing response resulting in neocollagenesis and tissue contraction occurs, while sparing the papillary dermis and epidermal layers of the skin (**Figure 1**).[12]

While traditionally a facial rejuvenation treatment, MFU-V has more recently used on the neck, chest and body to promote skin tightening and mild-to-moderate lifting in the appropriate candidate. With little to no downtime, MFU-V is one of the most in-demand non-surgical skin tightening treatments available. Results typically appear within 3-6 months and usually only require one or two treatments, making it an attractive modality for patients. Adverse events including pain, erythema, bruising and swelling are typically transient and mild, making this an excellent treatment in the appropriate patient looking to improve skin quality while managing a busy schedule.

Non-Invasive Radiofrequency

Radiofrequency (RF) energy is a form of electromagnetic current that can be delivered through various tissues including skin, fat and muscle to generate thermal energy.[13] Unlike lasers which target chromophores, RF generates heat because of different tissue resistance or impedance to the electromagnetic current giving desired therapeutic benefits.[12] When RF is applied to skin and soft tissue, contraction occurs secondary to (1) cleavage of hydrogen bonds in collagen triple helix leading to shortening and thickening of collagen fibrils and (2) initiation of a wound healing cascade to trigger neocollagenesis, neoangiogenesis and elastin reorganization over the subsequent 3-4 months.[1]

While the first RF device approved in 2002 was monopolar in nature (ThermaCool®; Thermage Inc., Hayward, Calif), more sophisticated devices including bipolar, multipolar and fractional RF now exist. Thermage®, Profound® RF, Exilis®, and Morpheus8® are just some of the devices available on the market today. The technology has been shown to be a safe and effective method to obtain soft tissue tightening and lifting of the skin on the neck, hands and body. RF technology is often combined with other modalities including microneedling (INFINI®, Lutronic, Goyang City, South Korea) or intense pulsed light (IPL) for improved cosmetic benefit.[14]

Contraindications include elderly patients with thin skin, autoimmune or collagen vascular disease, smoking, patients on anti-inflammatory medications (which may impair collagen remodeling) and the presence of a pacemaker or other implantable device.[1] In addition to skin tightening, RF devices are being used for fat reduction, and will likely continue to see expanded cosmetic indications in the future.

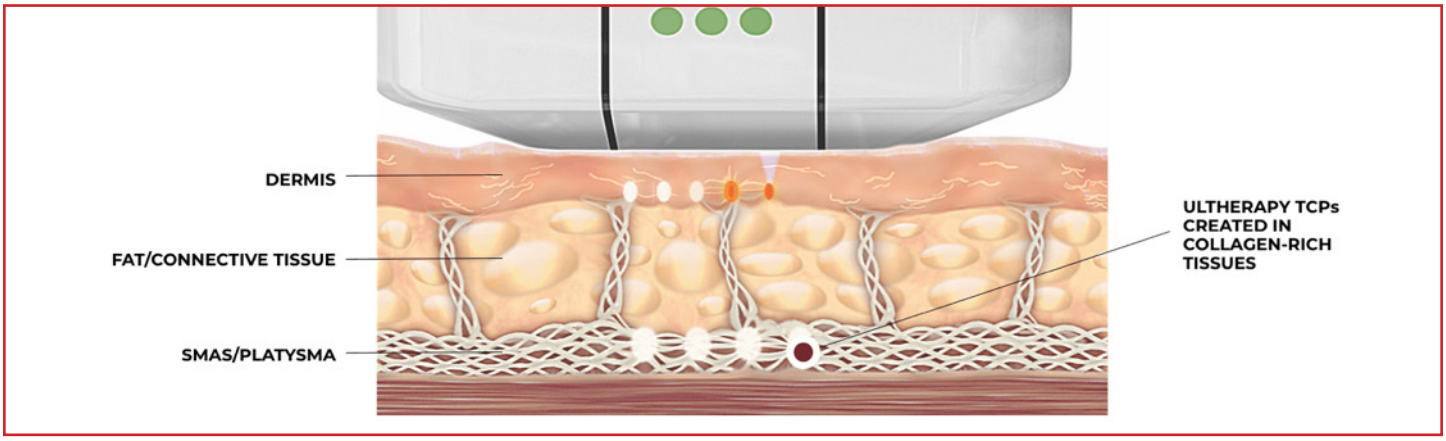

Figure 1. *Proposed Mechanism of Action of Ultherapy®. Microfocused ultrasound precisely targets dermal and subcutaneous tissues to create thermal coagulation points (TCPs), heating tissues to the optimal temperature for collagen contraction, denaturation and neocollagenesis. Merz Aesthetics, www.Ultherapy.com*

Conclusions

As patient demand for non-invasive skin tightening continues to grow, further technologies and innovations will likely emerge. It is important to note that neocollagenesis, elastin reorganization and the resulting lift or tightening effect does take time and often requires a series of treatments. Depending on the modality used, results may take 3-6 months to fully materialize, thus many of the above procedures are best suited to patients who are properly counselled on goals and expectations of treatment results.

As aesthetic specialists, in addition to offering novel treatments and procedures, it is also important to practice restraint where appropriate. The clinician must identify the limitations of each treatment modality and patient selection remains of utmost importance. Adverse effects including infection, skin necrosis, and scarring are possible with each of the technologies. Non-invasive skin tightening treatments may be suitable for those seeking modest-to-moderate improvement, with surgery still being the gold standard in many cases. Setting realistic expectations is of paramount importance to ensure positive outcomes, optimal patient satisfaction and to avoid disappointment.

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ONYCHOMYCOSIS

Onychomycosis is the most common nail disease, affecting about 6.7% of the general Canadian population, and as much as half of the population over 70 years old.[1,2] It can be categorized into various subtypes, and can range from mild to severe, with varying degree of hyperkeratosis, onycholysis, and discoloration (**Table 1**). Dermatophytes are the most pathogenic. Non-dermatophytes molds (NDMs) can include Scopulariopsis brevicaulis, Acremonium spp., Aspergillus spp. Fusarium, and Neoscytalidium, and are more common in warmer climates.[3] Yeast such as Candida can also be a cause. Risk factors include nail trauma, diabetes, psoriasis, genetics, immunosuppression, obesity, smoking, and advanced age[4,5]. Onychomycosis can at times cause significant pain, and psychological distress due to its often disfiguring nature. Given the older patient population, late presentation to a dermatology office, sometimes decades later, treatment can often be difficult. This can be compounded by presentations such as the dermatophytomas, which presents with abscess with white, yellow, orange or brown longitudinal streaks[6].

	Organism	Features
Distal-lateral subungual	*Trichophyton mentagrophytes* *Trichophyton rubrum* *Epidermophyton floccosum*	Most common
Superficial	*T. mentagrophytes* *T. rubrum*	
Proximal subungual	*T. rubrum* *Aspergillus* *Fusarium*	Debris in proximal nail fold *Possible immunodeficiency

***Table 1**. Patterns of onychomycosis and causative organisms; courtesy of Amy Cao, MD*

Differential diagnosis

Other nail diseases can often be confused for onychomycosis. It is always prudent to establish a diagnosis prior to treatment, as it is essential for treatment success, especially if multiple diseases need to be treated concomitantly.

Psoriasis can be very similar, but may also present with pitting and oil drops, which is not seen in onychomycosis. A systematic review found 18% of patients with psoriasis had concomitant onychomycosis compared to 9.1% in the general population.[7]

Lichen planus can feature dorsal pterygium, longitudinal ridging, and nail thinning.

Yellow nail syndrome which is characterized by the yellow nails of the hands and feet, with no cuticles.

Onychogryphosis – which is the thick ram horn like curve of the nail that can often be easily identified.

Retronychia is a distinct thickened opaque yellow great toenail due to ingrowth of proximal nail plate.

Nail digital dermoscopy can be used in the diagnosis of onychomycosis and when these images are evaluated the most common patterns seen include a jagged proximal border with spikes in the onycholytic area, and striae with blurred matte discoloration that resemble the Aurora Borealis.[8]

Investigations

Nail clippings and subungual debris should always be collected prior to treatment. Unfortunately, many patients have received treatment from another physician without having confirmatory testing. Approximately two-thirds of dermatologists test before treatment; conversely, half of family practitioners almost never test.[9] This adds an element of complexity to disease management, and the clinician should try to collect a sample of nail in which no antifungal treatment has been recently initiated.[10,11] To increase the yield, the patient can collect nail clippings at home after softening the nail with a keratolytic cream for one month. The nail can be cleaned with 70% isopropyl alcohol, and then clipped. The patient should be reminded that the debris that was under the nail can also be collected in a sterile urine container and sent for culture. The culture can take up to 6 weeks for results and is considered the gold standard as it can confirm fungal viability unlike histopathology. An additional sample can be sent for histologic evaluation with periodic acid-Schiff staining (PAS), which in a recent study of 631 nail samples was found to be the most sensitive single test for the diagnosis of onychomycosis at 82%, followed by culture (53%) and direct microscopy (48%) Combining both methods can increase the sensitivity to 96%.[11]

Alternatively, the specimen may be viewed on microscopy after it is placed on a slide with a potassium hydroxide 10% wet mount solution. Although microscopy will not identify the causative organism and has low sensitivity (48%), it is a quick method that can be performed in clinic.[12] Flow cytometry and polymerase chain reaction can also be used but is much more expensive.[13]

Treatments

In studies, a mycological cure (negative KOH and culture) is often compared to a clinical cure (100% visually normal nail). However, in practice the aim for most patients is a normal nail. A complete cure might not be possible in severe disease, or in patients with comorbidities that can retard the growth of the nail, especially if they are older or have infections from nondermatophyte molds (NDMs)[14].

An important aspect in the management of onychomycosis is setting appropriate patient expectations. Patients should understand that nails will likely still look the same after finishing oral therapy and may take 12-18 months to normalize. Photos can also be taken at the start of therapy, and then compared at the 12-month mark to validate that the proximal nail edge is growing normally. The FDA recommends a 5-mm growth of a healthy nail at 9 months post-treatment as proper response.[15]

The most successful treatment approach should combine topical and oral treatments. Terbinafine was found to be moderately superior to azoles in both mycological and clinical cure for onychomycosis according to a Cochrane review in 2017.[16] Itraconazole, however, offers a broad antifungal spectrum as compared to terbinafine against NDMs, and *Candida spp*, and can be considered in these cases.[17] In a recent meta-analysis looking at mycotic cure rates, azoles, such as itraconazole, were found to deliver superior efficacy when dosed continuously compared with pulse dosing (69% vs 63%).[18] Baseline and follow-up bloodwork is controversial, but recommended according to the manufacturer's product monograph.[19] In a double-blind study involving 151 patients, mycological and clinical relapse rates were more frequent in the itraconazole group than the terbinafine group.[20] A regimen including booster therapy of an additional month of terbinafine or up to nine months of pulse itraconazole has been elucidated in the literature.[21] This management approach is typically reserved for those patients with slow growing nails, greater than 2 mm of thickness of the nail plates,

	Dosing	Side effects	Monitoring
Terbinafine	250 mg PO q.d. x 6 weeks for fingernails x 12 weeks for toenails Pulse (not approved): 250 mg PO q.d. x 4 weeks, 4 weeks break, repeat x 1	Nausea, vomiting, dizziness, headache, taste disturbance, rash	Elevated transaminase Rare neutropenia
Itraconazole	200 mg PO q.d. x 6 weeks for fingernails x 12 weeks for toenails Pulse: 200 mg PO b.i.d. x 1 week per month x 2 months for fingernails x 3 months for toenails	Nausea, vomiting, dizziness, headache, upper respiratory tract infection, rash *Congestive heart failure	Hypokalemia Elevated transaminase Elevated triglycerides
Efinaconazole	Daily to toenails for 48 weeks	Burning and itching at application site, ingrown toenails	

***Table 2**. Simplified common modalities of treatment and dosing for adults with onychomycosis; courtesy of Amy Cao, MD*

lateral and/or matrix involvement, immunosuppressed, or with surface area involvement of more than 75% of the nail plate.[22,23]

A Cochrane review by Foley et al. in 2020 for mild-to-moderate toenail onychomycosis found that efinaconazole 10% topical solution is superior to placebo.[24] It should be considered the sole modality of treatment only when the onychomycosis involves less than 50% of the nail plate and does not implicate the matrix.[25] An adjunctive topical antifungal can also be helpful. Complete cure vs mycological cure with topicals is highest with efinaconazole at approximately 17.8% of patients achieving a complete cure on active treatment vs 3.3% of patients who received the vehicle. Mycologic cure was achieved by 55.2% of patients on active treatment compared with 16.8% of patients who received placebo. With tavaborole, 6.5% of patients on active treatment vs 0.5% on placebo achieved complete cure and 31.1% on active treatment (vs 7.2% receiving the vehicle) achieved mycologic cure. In a study of ciclopirox, 5.5% of patients on active treatment vs 0.9% receiving the vehicle were able to achieve a complete cure and 29% of patients on active treatment with ciclopirox were able to achieve mycologic cure compared with 11% of patients who received the vehicle.[26-28] Children tend to show excellent response to topical agents as monotherapy because of their faster growing and thinner nails. In severe disease, a recent study found that efinaconazole resulted in 65% and 40% mycological vs complete cure rates, respectively, at the 52-week follow up.[31] For adults, oral terbinafine, with topical efinaconazole, and topical antifungals should be used together for the best chance of cure. In addition, proper hygiene should be taken, and a topical keratolytic (i.e.. urea) can also be added to increase the efficacy. Also, recurrence was significantly lower in patients receiving topical antifungal prophylaxis than in those not receiving prophylactic treatment following oral terbinafine ($p < .001$) once a week for prophylaxis.[29]

Luliconazole 5% solution has very low evidence for a complete cure. Lasers such as Nd:YAG have been used to eradicate fungi by heating the affected tissue. Only three studies compared 1064-nm Nd:YAG laser to sham or no treatment and found little or no mycological cure after one year.[16] Photodynamic therapy also has a paucity of evidence to support its use.[30] Lasers should therefore not be the primary method of treatment but can be considered an adjunct should pain tolerance and cost not be limiting factors for the patient.

Given that onychomycosis often occurs in a warm and moist environment, any concomitant hyperhidrosis needs to be managed as well. The feet should be dried well after a shower, and some clinicians suggest using a hair dryer to be efficient. Patients should be reminded to wear 100% cotton socks, to bring an extra pair with them to the gym or on a hike, and to wash them with very hot water after use. Sandals should be used when walking to a swimming pool or at the gym, and, in general, patients should try to find less occlusive footwear. Patients should be encouraged to discard old footwear after treatment to prevent reinfection. Debridement can be ongoing during active treatment and result in higher clinical cure rate than just therapy alone.[31] Active tinea pedis

should also be treated with topical agents. It may also be prudent to determine if family members have onychomycosis or tinea pedis as they should be treated as well.

Conclusion

Onychomycosis is a common fungal infection that may require chronic treatment for months to years. It is always recommended to perform a culture and/or PAS prior to initiating treatment. Clinicians are encouraged to use multiple treatment modalities as well as post-treatment prophylaxis as the disease may be difficult to cure.

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PRURIGO NODULARIS

Introduction

Prurigo nodularis (PN) is a chronic, inflammatory skin disease highlighted by firm hyperkeratotic nodules and severe, unrelenting pruritus. It can affect both men and women of all ages. PN has a significant burden of disease, with a reduction in quality of life, sleep disturbances, anxiety, and depression. PN remains a challenging condition to control for many patients with currently no approved medications in Canada for its treatment. This may change however with some emerging therapeutic agents actively being investigated.[1,2]

Pathophysiology

The etiology and pathogenesis of PN remain unknown but current research postulates that PN is related to both immune and neural dysregulation. The neural dysregulation is supported by increased levels of pan-neuronal marker protein gene product, and nerve growth factor in PN patients. It is also supported by increased levels of known pruritic cytokines of calcitonin-gene related peptide, substance P, and vascular endothelial growth factor (VEGF). In terms of immune dysregulation, PN is thought to be a TH2 response, showing increased infiltrates of eosinophils, T-lymphocytes, and mast cells. These cells contribute to the release of a wide range of pro-inflammatory cytokines including, but not limited to, eosinophil cationic protein (ECP), eosinophil derived neurotoxin (EDN), eosinophil protein X (EPX), major basic protein (MBP), Interleukin (IL)-4, IL-31, and prostaglandins.[3] Understanding the pathophysiology can help explain the rationale for the use of certain treatments in PN. Hopefully, as researchers better understand the pathways involved in PN, more effective and targeted therapies will be developed.

Comorbidities

There are a variety of comorbidities that have been associated with PN. These include many of the same associations that have been linked to chronic pruritus, including atopic dermatitis, anxiety/depression, diabetes, renal disease, Hodgkin's lymphoma, HIV, iron deficiency anemia, COPD, inflammatory bowel disease, and hepatitis. In general, more research and larger studies are required to further explore the associations between these comorbidities and PN to determine if there is a potential casual link.[4]

Clinical Appearance and Differential Diagnosis

PN presents with characteristically firm, hyperkeratotic, excoriated nodules, often clustered together on at least two different extensor surfaces.[5,6] (**Figure 1-3**) The differential diagnosis for PN includes pemphigoid nodularis, actinic prurigo, hypertrophic lichen planus, neurotic excoriations, dermatotillomania, arthropod bites, scabies, multiple keratoacanthomas and atopic dermatitis.[7]

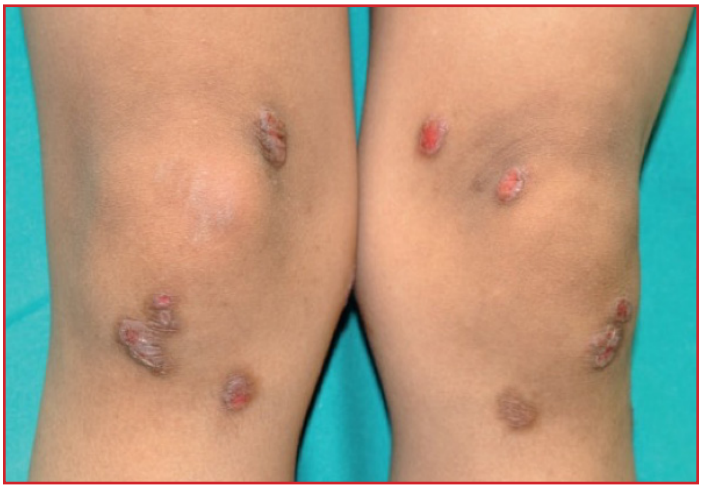

Figure 1. *PN on a patient's knees; Bolognia 4th edition*

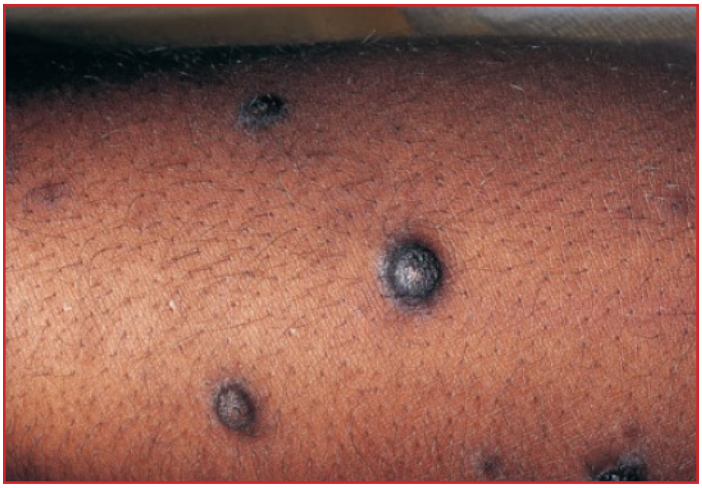

Figure 2. *PN on a patient's leg; Bolognia 4th edition*

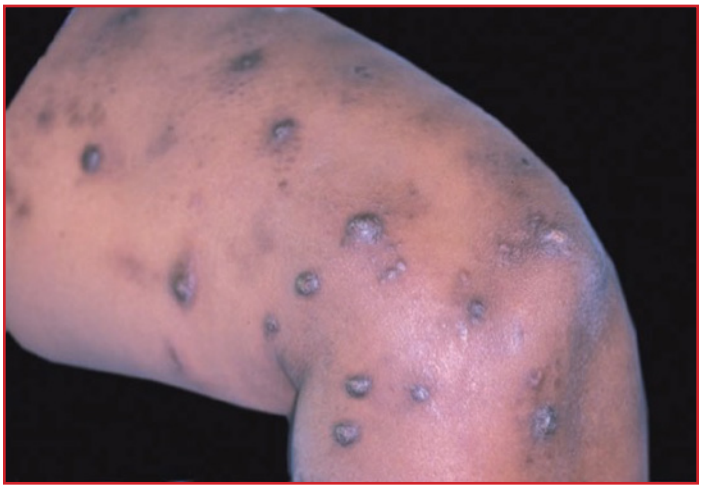

Figure 3. *PN on a patient's arm; Fitzpatrick 8th edition*

Clinical Work up

PN is primarily a clinical diagnosis of intense pruritus lasting 6 weeks or longer with the associated hyperkeratotic nodules. A skin biopsy may not always be necessary, but histology shows orthohyperkeratosis, irregular epidermal hyperplasia, hypergranulosis and an increased number of T-lymphocytes, eosinophils, fibroblasts, and capillaries.[3,7] It is generally recommended that patients suspected of having PN obtain a complete blood count (CBC), a liver function test and a renal function test. Additional consideration for the screening of thyroid function, hemoglobin A1c, human immunodeficiency virus, hepatitis B and C serologies is suggested and may be warranted based on risk factors and a review of systems for the patient. In addition to this, general screenings for an underlying etiology of pruritus can also be investigated if deemed appropriate which include serum protein electrophoresis with serum immunofixation, urinalysis, a chest x-ray, iron studies and stool exam for ova and parasites. Finally, age-appropriate malignancy screening should be up to date, especially if the pruritus has been going on for less than one year.[3]

Management

Treatment of PN remains a challenging task with significant variability in the approach to disease management. All treatments are considered off-label as there are currently no approved targeted therapies for PN. Newer, emerging systemic therapies are currently being investigated in phase 3 clinical trials[7,8] and may soon be available as treatment options. Current treatment modalities tend to work by targeting either the neural or immunological component of PN. In general, treatment can be divided into four categories: topicals, local/procedural, phototherapy, and systemic options.

Topicals

The most used first-line agent for PN is high potency topical steroids. Other treatment options studied including pimecrolimus, calcitriol, topical anesthetics, and capsaicin. **Table 1** provides a summary of these various options and different supporting evidence for them. In the writer's opinion, these topical agents do provide some benefit, but are typically less effective for moderate-to-severe cases.

Local/Procedural

Another commonly used 1st line therapy for PN is intralesional triamcinolone acetonide. This option works locally to reduce the size of nodules and decrease pruritus, but can be quite labour-intensive for severe, widespread disease. Other local and procedural options include cryotherapy and excimer laser.[3,7,8] **Table 1** provides more detailed summary of these options.

Phototherapy

Phototherapy can be an effective treatment option for some patients and is an overall a very safe modality. It can be particularly useful in many of the PN patients that have a more complex medical history where drug interactions and comorbidities can be difficult to work around. Phototherapy access and feasibility limits its use overall, and for some it still may not be sufficient at controlling their pruritus.[3,7] **Table 1** illustrates some further data regarding this option.

Medication	Potential Dosing Regimen	Efficacy	Additional notes
Topicals			
Corticosteroid creams, ointments, lotions	Medium-high potency b.i.d. prn	-Often insufficient as monotherapy -Helpful for mild disease	-Common 1st line agent, sometimes used under occlusion (e.g. with wraps or Unna boot)[3]
Corticosteroid tapes (e.g. betamethasone valerate 0.1% tape, flurandndrenolide tape)	Medium-high potency	-pilot study with 12 patients -Has been shown to reduce pruritus and flatten nodules[9]	-Allows for sparing of non-lesion skin -acts as physical barrier to prevent scratching -expensive
Calcineurin Inhibitors	Tacrolimus or Pimecrolimus b.i.d. prn	-RCT compared to HC 1%, with 30 patients -Has been shown to reduce itch[10]	-Potentially expensive -Good side effect profile
Capsaicin	0.025%-0.3% 4-6x per day	Mixed results. One study has shown potential ability to reduce itching and allow healing in 33 patients[11]	-Works by depleting neuropeptides in small sensory cutaneous nerve fibres -High application frequency -Potential significant skin irritation or burning
Calcipotriol ointment	applied b.i.d.	-RCT with 10 patients -Reduced number and size of nodules compared to betamethasone valerate 0.1%[14]	
Topical Anesthetics (Pramoxine 1%, Lidocaine Spray, Compounded topical anesthetic creams	-Once daily-twice daily application -Compounded topical ketamine (5-10%), amitriptyline (5%) and lidocaine (5%) in lipoderm cream t.i.d.	-Anecdotal evidence -retrospective review of compounded ketamine, amitriptyline, lidocaine showed significant mean improvement in Pruritus Numeric Rating Scale[28]	-theorized to work via modulation of N-methyl-D-aspartate glutamate receptors and sodium channels
Topical Cannabinoid	0.3% cream containing palmitoylethanolamide	-open application study; 14/22 patients demonstrated reduction in itch[32]	-minimal side effects
Local/Procedural Therapies/Phototherapy			
Intralesional Triamcinolone Acetonide (ILTA)	5-10 mg/mL injections directly into nodules q 4,6,8 weeks	Anecdotal evidence. case reports[12,13]	-commonly used treatment modality -difficult for generalized prurigo nodularis
Liquid Nitrogen	Applied directly to lesions q 4,6,8 weeks	-Anecdotal evidence -Case report[13]	-can be used in conjunction with ILTA
Narrowband UVB, PUVA	2-3x per week	-Numerous studies have shown to help reduce itching and improve lesions of PN as monotherapy or in conjunction with other therapies[15,16]	-good options for patients that cannot take oral medications due to underlying comorbidities or potential drug-drug interaction -can be adjunctive therapy -may not be feasible for patient
Excimer Laser, 308nm	Once-weekly	-compared to clobetasol ointment once daily showed significant improvement at week 34[17]	-not readily available -expensive

***Table 1**: topicals, local and phototherapy for treatment of prurigo nodualris. b.i.d.: twice daily; prn: as needed; t.i.d.: three times daily; UVB: ultraviolet B; PUVA: psoralen + ultraviolet A.; courtesy of Daniel Wong, MD, FRCPC*

Systemic Medications

Given the severity of many cases of PN, topicals and local agents are often not sufficient for fully controlling the symptoms of PN. As a result, many different systemic agents have been studied and used historically. These include immunosuppressants such as methotrexate, cyclosporine, and mycophenolic acid; neuromodulators including gabapentinoids, amitriptyline, antidepressants and thalidomide, and newer oral agents including aprepitant and serlopitant.[3,7,8] These medications deliver various levels of efficacy and are also associated with differing side effect profiles. **Table 2** provides a summary of many of these agents. Antihistamines have typically been ineffective and generally are not recommended unless comorbid histamine mediated conditions are suspected.[3,7]

Emerging Therapies

There are several medications currently being investigated for treatment of PN, some of which are showing promising early results. One such agent, nemolizumab[33], has recently gained "breakthrough therapy" designation by the FDA for treating PN. This process is designed to expedite the development and review of drugs that are intended to treat a serious condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on clinically significant endpoint(s).[34] Nemolizumab is a monoclonal antibody targeting IL-31, a proinflammatory cytokine upregulated in PN patients. Phase II studies have shown a significant reduction in pruritus scores (numerical rating scale [NRS]) in the nemolizumab treatment arm compared to the placebo group at 12 weeks. This same study also demonstrated improvements in quality of life, and a reduction in number of PN lesions.[31] Currently, nemolizumab is being investigated in phase III clinical trials.

Another newer therapy emerging as a potential effective option for PN is dupilumab. Dupilumab is a monoclonal antibody that works by inhibiting IL-4 and IL-13, which are both proinflammatory cytokines known for contributing to pruritus. Dupilumab is more well known for its treatment of atopic dermatitis but has shown in several case reports and case series to be effective at improving PN.[30] Like nemolizumab, it is also undergoing phase III clinical trials.

Other emerging treatment options being investigated for PN include oncostatin M beta receptor, opioid antagonists, and cannabinoids.[7] [7]. **Table 2** provides additional information about some of these newer therapies.

Conclusion

PN is chronic inflammatory skin disease that is often clinically challenging. Although strides have been made in recent years with understanding this condition and with the development of newer therapeutic agents, further research into the pathophysiology and targeted treatment modalities are still needed to better understand PN.

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Medication	Potential Dosing Regimen	Efficacy	Additional notes
Oral Agents			
Thalidomide	100 mg PO daily	-multiple studies showing efficacy[18,19]	-poor safety profile (especially peripheral neuropathy, teratogenicity, depression, nausea, dizziness, sedation) -not commonly used -thought to work on central neural system, and as immunomodulator
Methotrexate	7.5 mg to 20 mg SC q weekly	-retrospective studies 13-patient study showed >75% reduction in prurigo nodularis area and severity index[20] 39-patient study showed disease response of 91% and 94% at 3 and 6 months respectively[21]	-common side effects of nausea, transaminitis, GI symptoms -mechanism of action for PN unknown
Cyclosporine	3 to 5 mg/kg daily	-case series -19 of 22 patients showed significant improvement with cyclosporine with maximal effect after 2-3 months[22,23]	-theorized to work via inhibition of IL-2 -nephrotoxicity, hypertensive risks with long term use
Pregabalin	75 mg daily	-prospective study -Complete response in 23 of 30 patients at 3 months[24]	-modulates neural gamma-aminobutyric acid signalling -side effects of sedation, headache
Gabapentin	300 mg/day initiated and gradually increased to 900 mg/day	-retrospective study -4 patients had partial or complete response at 3-4 months[25]	-modulates neural gamma-aminobutyric acid signalling -side effects of sedation
Amitriptyline	10 to 60 mg	-beneficial effect in 17 PN patients[26]	-monoamine oxidase inhibitor -inhibits uptake of norepinephrine and serotine -sedative
SSRI inhibitor	Paroxetine 10 to 60 mg daily Fluvoxamine 25 to 150 mg daily	-17 patients showed partial clearing and 14 showed complete lesion healing[27]	-antidepressants -side effects: insomnia, rashes, head aches, sexual dysfunction, GI upset, CNS, cardiovascular
Serlopitant	5 mg daily	-RCT with 127 patients -significant reduction from baseline at 8 weeks in Visual Analog Scale (VAS) compared to placebo at 8 weeks[29]	-neurokinan-1 receptor antagonist -targets substance P -well tolerated, mild-moderate adverse events only -being investigated for chronic pruritus -expensive
Biologics and Emerging Therapies			
Dupilumab	600 mg SC followed by 300 mg SC q 2 weeks	-multiple case series and case reports demonstrating reduction in NRSi (numerical rating scale itch)[30]	-IL4/IL-13 antagonist -excellent safety profile -not FDA approved and expensive -currently in phase 3 clinical trials
Nemolizumab	0.5 mg/kg SC at baseline, week 4, and week 8	-12 week, RCT Phase 2 trial 70-patient study, showing significant reduction in NRS in treatment arm compared to placebo[31]	-works as an IL-31 receptor antagonist, thus lowering IL-31 in PN patients -Currently in phase 3 trials -side effects of GI and MSK symptoms -granted Breakthrough Therapy designation for treatment of pruritus in prurigo nodularis
Oncostatin M (OSM) beta receptor	KPL-716 monoclonal antibody (Vixarelimab) 720 mg SC loading dose followed by 360 mg q weekly.	-data pending -Press release from Kiniska reports statistically significant reduction in WI-NRS at week 8.	-currently in phase II clinical trials -pro-inflammatory signaling molecule similar to IL-6

***Table 2**: Systemic therapies for PN. PO: orally; SC: subcutaneous; SSRI: selective serotonin reuptake inhibitors; GI: gastrointestinal; MSK: musculoskeletal; CNS: central nervous system; RCT: randomized control study; courtesy of Daniel Wong, MD, FRCPC*

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THE CURRENT LANDSCAPE OF ARTIFICIAL INTELLIGENCE IN DERMATOLOGY

The role of artificial intelligence (AI) in medicine is evolving rapidly. The pace at which technology is progressing necessitates that we understand AI, and specifically, its role in the management of dermatological disease. The objective of this article is to provide resources for further learning about the role of AI in dermatology, and to describe its current landscape and future directions.

Background

For many clinicians, "AI" might as well stand for "altogether impossible". As technology advances, it will be increasingly important for us to understand how to interpret scientific articles about AI, not just for our own learning, but also for the purpose of teaching trainees or engaging with peers at journal club. To this end, *JAMA* published a users' guide entitled, "*How to Read Articles that Use Machine Learning*".[1] This can be found on their "Machine Learning" hub,[2] which has other relevant articles and multimedia content, including "*On Deep Learning for Medical Image Analysis*,"[3] and its accompanying video, "*Understanding How Machine Learning Works.*"[4] Recently, *CMAJ* published a series of three articles on machine learning in health care, exploring its implementation[5], problems in deployment[6], and evaluation[7].

AI is conventionally defined as "the use of machines to imitate intelligent human behaviour."[8] Machine learning (ML) and deep learning (DL) are subsets of AI (**Figure 1**).

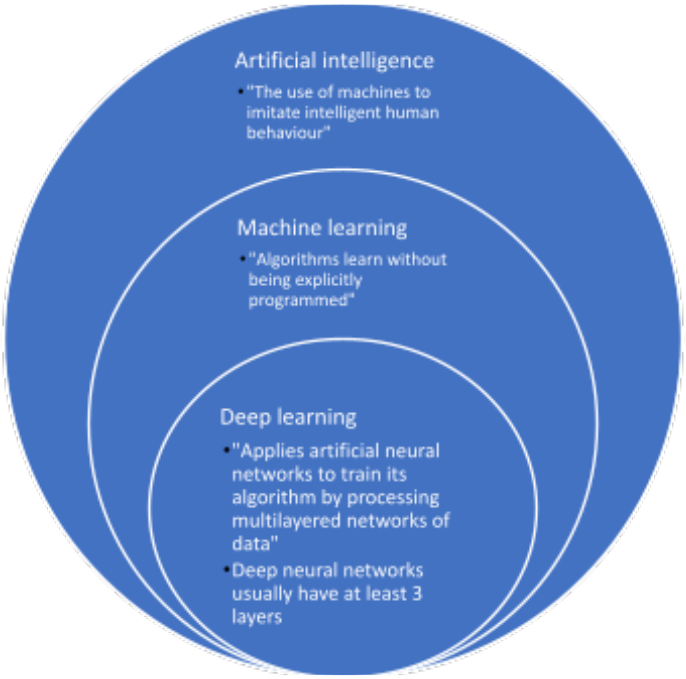

Figure 1. *Definitions of artificial intelligence, machine learning, and deep learning. Adapted from JAAD.*[8,9]

Augmented intelligence (AuI) describes the interaction between clinicians and artificial intelligence (**Figure 2**). With the expansion of AI research in dermatology, in 2019, the American Academy of Dermatology (AAD) issued a position statement on AuI which emphasized the assistive role of AI for clinicians and presented four aims of AuI: (1) enhancing patient experience, (2) improving population health, (3) reducing costs, and (4) improving the professional fulfillment of care teams. The position statement puts forth recommendations for the development of AuI, with the goal of providing high quality care to patients. Key issues include model development, clinical deployment, post-marketing surveillance, engagement, education, privacy and medico-legal issues, and advocacy.[10]

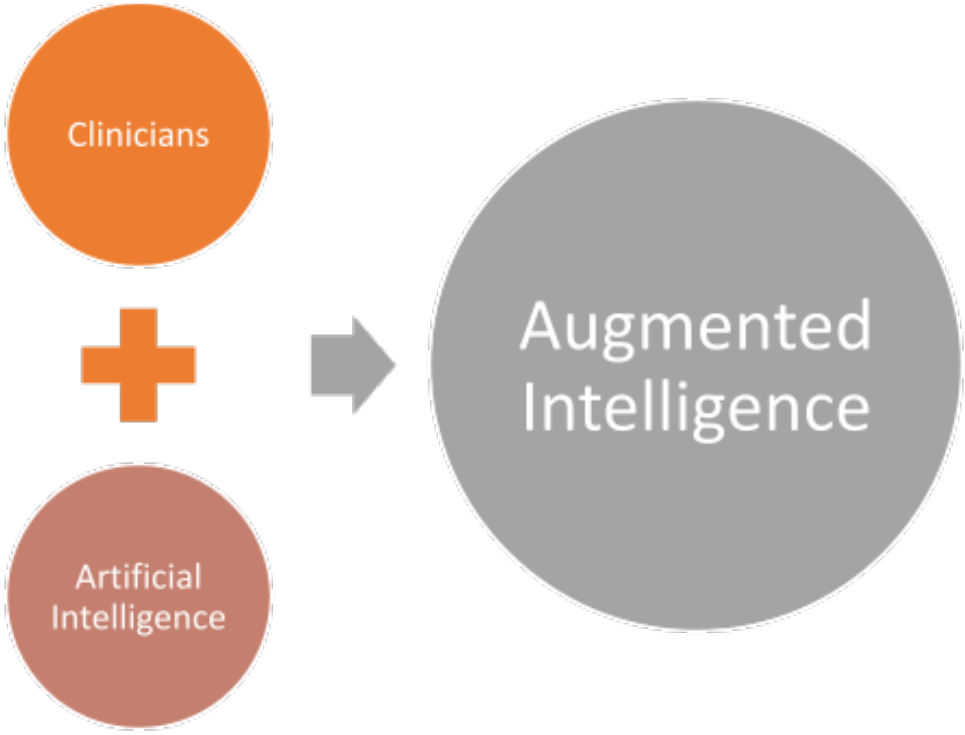

Figure 2. *Augmented Intelligence; courtesy of Rebeca Pinca, MD.*

AI applications in dermatology

Several comprehensive reviews on the use and application of AI in dermatology have been published,[8,9,11,12] including a review by Canadian colleagues Gomolin et al.,[12] and selected studies of interest will be highlighted below.

The most common application of AI in dermatology is in the diagnosis of malignant lesions, including keratinocyte carcinomas and melanoma. In 2017, researchers at Stanford published a paper in *Nature* describing a deep convolutional neural network which achieved performance on par with 21 dermatologists at classifying keratinocyte carcinomas versus benign seborrheic keratoses, and malignant melanomas versus benign nevi, based on clinical and dermoscopic images.[13] Since then, there have been other similar papers published.[14,15]

One of the first prospective diagnostic accuracy studies comparing a dermatologist's clinical examination at the bedside, teledermatology, and non-invasive imaging techniques (FotoFinder®, MelaFind®, and Verisante Aura) in the diagnosis of melanoma was done by Canadian colleagues MacLellan et al. They recruited 184 patients and 209 lesions were imaged, assessed, and excised. Skin specimens were assessed by 2 blinded pathologists for the gold standard comparison. Histopathologic examination resulted in diagnoses of 59 melanomas and 150 benign lesions. Sensitivities and specificities were, respectively, MelaFind (82.5%, 52.4%), Verisante Aura (21.4%, 86.2%), FotoFinder Moleanalyzer Pro (88.1%, 78.8%), the teledermoscopist (84.5%, 82.6%) and the local dermatologist (96.6%, 32.2%). The authors note that the high sensitivity of some non-invasive devices in the diagnosis of melanoma is consistent with prior studies. However, they comment that low specificity and low diagnostic accuracy preclude some of these machines from replacing a dermatologist's clinical experience in selectively choosing which lesions to excise. When the FotoFinder Tuebinger was used as an aid to the clinical diagnosis, both of the melanomas missed by the local dermatologist were identified, and when it was used as an aid by the teledermatologist, missed melanomas were reduced from 4 to 3. This symbiosis between clinician and AI illustrates the potential benefits of augmented intelligence. The practical limitations to using these devices in a clinical setting include size, location, and Fitzpatrick skin phototype (skin types higher than III were excluded due to limitations of the machines for melanoma diagnosis in patients with higher phototypes).[16]

Canadian colleagues Breslavets et al. compared the ability of a dermatologist, two laypersons (science students) and an artificial neural network (ANN) to estimate

the percentage body surface area of psoriasis involvement. The ANN had a mean percentage error (MPE) of 8.71% (SD, 6.70%; 95% CI, 7.64%-10.02%) compared with the physician's MPE of 28.16% (SD, 22.69%; 95% CI, 24.76%-32.61%). This study showed that AI applications may potentially play an important role in aiding in the triage of patients and that the technology employed via ANN may provide a more consistent assessment of skin areas affected by psoriasis through calculating the percentage of the affected skin, compared with routine measurement by the palm method.[17]

Other potential applications of AI in dermatology include onychomycosis,[18] alopecia areata,[19] lupus,[20] ulcers,[21] and acne.[22]

Precision medicine is another area with potential AI applications in dermatology. A review of ML in dermatology found that it is being applied to electronic medical records, patient laboratory data, and genomic data from next-generation sequencing to study the genetic basis of diseases; to identify associations between comorbidities, risk factors, and disease prognosis; and to design and predict responses to pharmacologic therapies. The authors describe potential applications including prediction of adverse drug reactions and responses to therapy in oncologic dermatology, autoimmune and rheumatologic skin disease.[23]

Numerous direct-to-consumer mobile applications are being developed with the aim of improving access to health care, especially in limited resource settings. A recent systematic review of diagnostic accuracy studies for algorithm-based smartphone apps to assess risk of skin cancer found that they were unreliable for detecting melanoma and other skin cancers.[24] There are benefits of a full cutaneous examination that would be limited with a direct-to-consumer app. It is common for patients to report a concern about a seborrheic keratosis, and after ruling out anything serious, clinicians may find another lesion of concern during their examination that the patient was either unconcerned about, or unaware of, due to difficulty in visualizing their back or other body areas. This may potentially cause delay in diagnosis of subtle lesions.

AI and health care disparities

It is important to ensure that health care disparities are addressed early in the implementation of AI in dermatology. One of the largest open-source public-access archives of pigmented lesions, the International Skin Imaging Collaboration: Melanoma Project, relies mostly on images of fair-skinned individuals and neural networks based on such training data sets may not be accurate in skin of colour.[25] While the incidence of melanoma is higher in this population, it is important to ensure that the accuracy of AI is high for all skin types. Han et al. performed a study to validate algorithms for the diagnosis of skin cancers by testing them on different data sets than those they were originally trained on.[26] They found that algorithms trained on Caucasian skin performed suboptimally when tested on data sets of Asian skin, as subtypes of melanoma differ in prevalence amongst skin types. Similarly, algorithms trained on Asian skin performed suboptimally when tested on data sets of Caucasian skin, as the appearance of BCC tends to differ amongst skin types.

Patient perspectives

As progress is made in evaluating the role of AI for clinical implementation, it is important to consider the perceptions and preferences of patients prior to its widespread use[27]. Nelson et al[28] published one of the first studies exploring this domain, specifically on the use of AI for skin cancer screening. They used a semi-structured interview technique for their qualitative study of 48 patients at the Brigham and Women's Hospital and the Dana-Farber Cancer Institute, 33% with a history of melanoma, 33% with a history of nonmelanoma skin cancer only, and 33% with no history of skin cancer. Half the patients were interviewed about a direct-to-patient AI tool and half were interviewed about a clinician decision-support AI tool. The most commonly perceived benefits of AI for skin cancer screening were increased diagnostic speed and health care access; the most commonly perceived risk was increased patient anxiety. Patients commented on the importance of physician compassion, empathy, eye contact, and human touch, as well as the AI's inability to answer follow-up questions, discuss treatment options, and educate and reassure patients. Ironically, the greatest strength of AI was perceived by patients to be more accurate diagnosis – and its greatest weakness, less accurate diagnosis. Three quarters of those interviewed would recommend AI to friends and family members. The vast majority (94%) emphasized the importance of symbiosis between humans and AI, highlighting the role of augmented intelligence.

Conclusion

AI will likely revolutionize the practice of medicine in the coming years, and it is therefore important that dermatologists are at the forefront of AI advances in dermatology. Zakhem et al. reviewed studies on AI and skin cancer, and only 41% had dermatologists as co-authors. Articles that included dermatologists described algorithms built with more images versus articles that did not include dermatologists (mean, 12,111 vs 660 images, respectively).[29] Currently, there are numerous limitations to the current landscape of AI in dermatology, including lack of extensive validation and prospective studies in clinical settings, lack of guidelines regarding ethics, concerns about lack of inclusivity and equal access, and potential funding biases in publications. However, AI advances on the horizon have the potential to be helpful tools in our clinical practices as we care for our patients.

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