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The Cover Shot
One of the excitements of SCUBA diving is meeting the vast number of marine lives. This is a collage of four different marine creatures taken during my dives in Bali and Ishigaki island. From top left to the bottom right, they are the nudibranch, peacock mantis shrimp, green sea turtle, and a clownfish dancing in the anemone.

Spotting the peacock mantis shrimp under a rock in Tulamben was a gasping moment. It was beautiful but dangerous, being able to deliver a powerful punch equivalent to a bullet! The ocean never fails to amaze the divers and keep us humble.

Dr Shirley Chiu-wai CHAN
MBBS (HK), MRCP (UK)
What is the Insight into Rheumatology in the 21st Century?

Dr Carmen Tze-kwan HO
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Past President, Hong Kong Society of Rheumatology
Editor

Rheumatology is a subspecialty of general medicine that only became well recognised in the 1970s in Hong Kong. There were only a handful of physicians interested in this new specialty, and yet polyarthritis as a symptom of many rheumatic diseases is one of the most commonly complained problems.

The 1950s brought corticosteroids to rheumatoid arthritis (RA) sufferers. It significantly reduced the inflammation, and this was the 'take up your bed and walk' drug. However, the long-term use of steroids also brings significant side effects to these patients. The next drug invention is non-steroid anti-inflammatory drugs like indomethacin and ibuprofen. They are the miraculous drugs to many people living with arthritis. However, they are the double-edged swords; some patients do not survive from severe gastrointestinal bleeding, and some die of renal failure. The history of using methotrexate to treat RA could be dated back to 1948. Aminopterin, an anti-folate agent, was used successfully to treat childhood leukaemia. Aminopterin was also studied in several RA patients in an observational study in 1951 by Gubner et al.1 Methotrexate, also an anti-folate agent, was used successfully to treat childhood leukaemia. Aminopterin was also studied in several RA patients in an observational study in 1951 by Gubner et al.1


References
NOW FOR ADULT PSORIATIC ARTHRITIS (PsA) AND ANKYLOSING SPONDYLITIS (AS)

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1. Cosentyx® Hong Kong Product Insert [Ref: EMA Apr 2016]

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Use of Cosentyx may increase the risk of serious endocrine system adverse reactions, including hypothyroidism. Patients should be monitored for the development of serious endocrine system adverse reactions. Use of Cosentyx may increase the risk of serious hematologic system adverse reactions, including hemolytic anemia and thrombocytopenia. Patients should be monitored for the development of serious hematologic system adverse reactions. Use of Cosentyx may increase the risk of serious skin and subcutaneous tissue adverse reactions, including skin cancer. Patients should be monitored for the development of serious skin and subcutaneous tissue adverse reactions. Use of Cosentyx may increase the risk of serious infectious adverse reactions, including tuberculosis. Patients should be monitored for the development of serious infectious adverse reactions. Use of Cosentyx may increase the risk of serious opportunistic infections. 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The Current Management of Psoriatic Arthritis – Early Diagnosis, Monitoring of Disease Severity and Cutting-Edge Therapies

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 30 April 2020.

BACKGROUND

Psoriatic arthritis (PsA) is a chronic immune-mediated disease with heterogeneous clinical manifestations including psoriasis, peripheral arthritis, axial disease, enthesitis, dactylitis and nail involvement. Up to 30% of patients with psoriasis will develop synovio-entheseal manifestations. In the majority of patients, the musculoskeletal symptoms develop after the cutaneous manifestations, but can also coincide with or precede (15%) the diagnosis of psoriasis. PsA is an important disease to recognise as it carries significant morbidity and disability. Furthermore, early diagnosis and prompt treatment are important as delay in treatment is associated with worse treatment outcomes.

SCREENING

Several screening tools have been developed to facilitate the early diagnosis of patients with psoriatic arthritis. These include the Toronto Psoriatic Arthritis Screening Questionnaire (ToPAS), Psoriasis Epidemiology Screening Tool (PEST), Psoriatic Arthritis Screening and Evaluation (PASE), and the Psoriasis and Arthritis Screening Questionnaire (PASQ)⁴-⁶. These screening tools have comparable sensitivity (82-97%) and specificity (73-93%) (Table 1). They can be used in the dermatology clinics or primary care offices to facilitate early identification of PsA patients.

Table 1. Screening tools for early diagnosis of psoriatic arthritis. (Adapted from Machado P.M, Raychaudhuri SP. Disease activity measurements and monitoring in psoriatic arthritis and axial spondyloarthritis, Best Pract. Res. Clin. Rheumatol.28 (2014) 711e728.)

<table>
<thead>
<tr>
<th>Screening tools</th>
<th>Description</th>
<th>Sensitivity/specificity</th>
</tr>
</thead>
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<td>Topas</td>
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<td>Sensitivity 87% Specificity 93%</td>
</tr>
<tr>
<td>PEST</td>
<td>Self-administered 5 items + joint diagram; Maximum score: NA</td>
<td>Sensitivity 97% Specificity 79%</td>
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<tr>
<td>PASE</td>
<td>Self-administered 15 items; Maximum score: 75</td>
<td>Sensitivity 82% Specificity 73%</td>
</tr>
<tr>
<td>PASQ</td>
<td>10 items + joint diagram; Self report</td>
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CLINICAL CHARACTERISTICS

Clinical Features

Five clinical subtypes of PsA have been described by Moll and Wright in 1973⁷. The oligo-articular subtype involving no more than four joints is the most common. Others include the symmetrical polyarticular subtype, distal subtype, arthritis mutilans and axial subtype. Other extra-articular features include enthesitis (e.g. plantar fasciitis and Achilles tendonitis), dactylitis and nail disease (pitting and onycholysis).

Laboratory Test

The majority of patients (95%) with PsA have a negative test for rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibody. Around 25% of patients are HLA-B27 positive. Acute phase reactants including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are used to assess disease activity.

Table 1. Screening tools for early diagnosis of psoriatic arthritis. (Adapted from Machado P.M, Raychaudhuri SP. Disease activity measurements and monitoring in psoriatic arthritis and axial spondyloarthritis, Best Pract. Res. Clin. Rheumatol.28 (2014) 711e728.)

Imaging Features

Radiographic imaging of the hands and feet may show joint erosion, joint resorption and new bone formation (Fig. 1). The pencil-in-cup deformities are observed in cases of arthritis mutilans. Ultrasonography can help to supplement diagnosis and disease activity assessment for arthritis, enthesitis and dactylitis.
In axial disease, radiographs of the spine and sacroiliac joints can be used to assess for sacroiliitis and para-marginal syndesmophytes, which are typically asymmetrical in PsA patients. Magnetic resonance imaging (MRI) can be used to evaluate disease activity and structural damage in the spine and sacroiliac joints.

**DIAGNOSIS**

The diagnosis of PsA is a clinical judgement based on clinical, laboratory and imaging assessment. There are no validated diagnostic criteria for PsA. The Classification Criteria for Psoriatic Arthritis (CASPAR) criteria (Table 2) published in 2006 has been designed to select patients for clinical trials and provide guidance for the physician.

**Pharmacological Treatment**

Over the past decade, the option of pharmacological treatments for PsA has expanded from non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and conventional disease-modifying anti-rheumatic drugs (csDMARDs) to include biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) which target specific cytokines and intracellular signalling pathway involved in PsA. Their efficacy in controlling disease activity and preventing disease progression has been proven in randomised controlled trials.

Treatment guidelines and recommendations have been published by several international organisations to guide physicians’ decisions in selecting the optimal treatment. These include the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) in 2015, European League Against Rheumatism (EULAR) in 2015, and American Association of Rheumatology (ACR) in 2018.

In general, a stepwise approach with a treat-to-target principle is advocated. The choice of treatment remains a shared decision between patients and physicians, and should also take into account of patients’ preferences, co-morbidities and costs.

**TREATMENT OPTIONS**

**NSAIDs and Glucocorticoids**

NSAIDs and local injection of glucocorticoids may be used to control symptoms of PsA. The physician should be cautious about the potential side effects of NSAIDs. The systemic steroid is generally avoided as it is associated with a risk of psoriatic flare upon steroid tapering and the risk of pustular psoriasis. When the systemic steroid is used, the lowest effective dose should be used (usually prednisolone < 7.5 mg per day).

**Conventional DMARDs**

Before the development of advanced therapies (bDMARDs and tsDMARDS), csDMARDs were used to treat PsA, including methotrexate, leflunomide, sulphasalazine and cyclosporin A. Their role has been increasingly challenged because of the scant evidence of their efficacy in peripheral PsA and because they do not affect radiological progression. csDMARDs are not useful in axial disease, enthesitis and nail disease.

Due to their low cost and universal availability, csDMARDs remain to be the first line of therapy for peripheral arthritis in the EULAR and GRAPPA guidelines, with the need for early escalation of therapy if adequate response cannot be achieved. On the contrary, the latest ACR guideline conditionally recommended TNF inhibitors as first-line therapy over csDMARDs except in patients with frequent serious infections or those who are contraindicated to TNF inhibitors. csDMARDs might also be considered as first-line in patients with mild disease, who prefer oral therapies and who want to avoid biologics.

**MANAGEMENT**

**Disease Activity Assessment**

In managing patients with PsA, a careful assessment of disease activity in the different symptom domains is important to guide treatment decision. Disease activity assessment includes assessing for the extent of skin involvement, peripheral arthritis, axial disease, enthesitis, dactylitis and nail disease. Different disease activity indices have been developed, including those that are specific to each domain or composite disease activity indices. Also, a treat-to-target approach aiming at low disease activity or remission is advocated guided by these disease activity indices (e.g. MDA and DAPSA).

**Non-pharmacological Treatment**

Non-pharmacological treatment includes patient education about the chronic nature of the disease and the importance of controlling inflammation and the prevention of joint damage. Lifestyle modification, such as weight reduction, smoking cessation, physical activity and stress management, is also crucial for the management of PsA. The screening and management of co-morbidities, especially metabolic syndrome and atherosclerotic cardiovascular diseases, are also important.
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Biological DMARDs and Other Advanced Therapies

Biological therapies targeting TNF, interleukin-17, interleukin 12/23 and the co-stimulatory pathways have been developed for use in PsA.

Anti-TNF agents (Infliximab, Adalimumab, Etanercept, Certolizumab and Golimumab) are recommended as the preferred first-line option when selecting a bDMARD based on long-term experience and well-established efficacy and safety balance. They are useful in both skin and peripheral joint involvement and can prevent radiographic damage.15 Combining a csDMARD with TNFi may have a role. However, most studies show that compared to biologic monotherapy. Combination therapy is no better in improving clinical symptoms, although there may be a role in improving drug survival14. Based on the studies in axial spondyloarthritis, anti-TNF is also effective in treating enthesitis, dactyliitis, and axial diseases15.

Secukinumab and Ixekizumab are the two bDMARDs targeting the IL-17 pathways currently approved for the treatment of PsA and are effective in both skin and musculoskeletal features.6,16,17 A recent head-to-head trial compared the efficacy of Ixekizumab with Adalimumab in biological-naïve patients showing the superiority of Ixekizumab.8 Ustekinumab, an antibody targeting the shared p40 subunit of IL12 and IL23, is effective for both skin and musculoskeletal manifestations with a more impressive response in skin manifestations9. Abatacept, a molecule that blocks the T cell co-stimulation pathway, has a moderate effect in treating the joint manifestation but only a modest effect on the skin in PsA10.

Targeted synthetic molecules acting against the JAK/ STAT pathway have been developed to treat autoimmune diseases, including PsA. Tofacitinib, an oral bDMARD with activity against JAK3 and JAK1, is approved for the treatment for PsA. Other JAK inhibitors, including Filgotinib (JAK1 inhibitor) and Upadacitinib (JAK1 inhibitor) are being studied in clinical trials for the treatment of PsA.

CONCLUSION

Psoriatic arthritis is a disease with heterogeneous manifestations occurring in up to 30% of patients with psoriasis and is associated with significant morbidity. Early diagnosis is assisted by screening questionnaires, facilitating early treatment to control disease activity and structural progression. Emerging therapies provide an effective means to control inflammation and prevent long-term joint destruction.

References


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<table>
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<tr>
<th>RAPID 1 OLE-RA¹</th>
<th>Mean DAS28 (ESR)</th>
<th>RAPID-axSpA²</th>
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<th>RAPID-PsA³</th>
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CIMZIA®, the biologic anti-TNF, has shown to be highly effective and safe in patients with RA, axSpA and PsA, achieving rapid and sustainable long-term effect.

MCHK CME Programme Self-assessment Questions

Please read the article entitled “The Current Management of Psoriatic Arthritis – Early Diagnosis, Monitoring of Disease Severity and Cutting-Edge Therapies” by Dr Shirley Chiu-wai CHAN & Dr Helen Hoi-lun TSANG and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 30 April 2020 Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. Musculoskeletal manifestations of psoriatic arthritis (PsA) occur only in patients with established psoriasis.
2. Screening of PsA is important, and several screening tools have been developed to be applied in dermatology clinics or primary care offices.
3. Enthesitis, dactylitis and nail disease are important extra-articular manifestations to assess in patients with PsA.
4. Most patients with psoriatic arthritis have a positive test for rheumatoid factor and/or anti-cyclic citrullinated peptide antibody.
5. The Classification Criteria for Psoriatic Arthritis (CASPAR) criteria is the ONLY gold standard for diagnosing patients with psoriatic arthritis.
6. The treatment of PsA follows a stepwise approach with a treat-to-target principle.
7. Conventional disease-modifying anti-rheumatic drugs (cDMARDs) are the first-line treatment for PsA because of their efficacy in controlling disease activity and halting radiographic progression.
8. Anti-TNF agents are recommended as the preferred option when selecting biological DMARDs based on long-term experience and well-established efficacy and safety balance.
9. There is a lack of head-to-head trial to directly compare the efficacy of different biological therapies in PsA.
10. Oral agents targeting small molecules such as PDE4 or the JAK/STAT pathway are available for the treatment of PsA.

Please return the completed answer sheet to the Federation Secretariat on or before 30 April 2020 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

The Current Management of Psoriatic Arthritis – Early Diagnosis, Monitoring of Disease Severity and Cutting-Edge Therapies

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Time to enhance our preparedness to handle trauma and stress-related disorders in Hong Kong

Immunoglobulin (Ig) G4-related Disease: What Do We Need to Know?

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INTRODUCTION

Immunoglobulin (Ig) G4 is the least abundant of the four subclasses of IgG and often considered an inhibitory or anti-inflammatory molecule found in patients with various autoimmune or allergic conditions. However, relatively little attention had been paid to this “minor” molecular until the discovery of its association with type I autoimmune pancreatitis in the early 2000s. Since then, many clinical entities have been found to be related to IgG4, and the new entity of IgG4-related disease (IgG4-RD) was born.

IgG4-RD remains an increasingly recognised immunemediated systemic disorder and involvement of almost every anatomical site has been reported. It is a fibro-inflammatory condition with characteristic histopathological features, and unifies what were previously thought to be unrelated individual organ disorders. Other examples of previous disease entities now under the diagnostic umbrella of IgG4-RD include Riedel’s thyroiditis, Ormond’s disease (idiopathic retroperitoneal fibrosis), Mikulicz disease (lymphoepithelial sialadenitis), Kuttner’s tumour (chronic sclerosing sialadenitis), and other “idiopathic” pseudotumours. Regardless of the organ involved, patients with IgG4-RD share similar clinical, serological and histopathological features that are key to its Diagnosis.

DIAGNOSIS AND PRESENTATION OF IgG4-RD

Various proposed diagnostic criteria and consensus papers on the pathology of IgG4-RD have been published. In brief, the Diagnosis of IgG4-RD is usually considered “definite”, “probable” or “possible” depending on the constellation of clinical, serological and, especially, histopathological findings. The recommended cut-off value for serum IgG4 level is 135 mg/dL. The three characteristic histological findings include: 1) dense lymphoplasmacytic infiltrate, 2) “storiform” or swirling fibrosis, and 3) obliterative phlebitis. IgG4 immunostaining should show >10 IgG4+ plasma cells per high power field and an IgG4+/IgG+ plasma cell ratio >0.4. In addition, patients who fulfil other organ-specific criteria are also considered to have a “definite” diagnosis. For example, organ-specific diagnostic criteria are available for conditions including IgG4-related–Mikulicz disease, sclerosing cholangitis and kidney disease. However, it is important to remember that elevated serum IgG4 levels are neither sensitive nor specific. Elevated serum IgG4 levels can be seen in a variety of other conditions such as malignancies, infections, or autoimmune disorders. Furthermore, IgG4+ plasma cells can be seen in a variety of other conditions and often masquerade various malignancies, infections or autoimmune disorders.

Patients commonly present with painless subacute swelling, organomegaly or organ damage. Constitutional symptoms are infrequent, although weight loss can occur especially with multi-organ involvement. The disease can have a multitude of clinical manifestations depending on the organ system(s) involved. IgG4-RD is infamously a great masquerade of many infective, malignant or autoimmune disease. It is often initially misdiagnosed as malignancies (presenting as “pseudotumours”) or may even be incidentally diagnosed during other radiological or histological examinations.

MANAGEMENT OF IgG4-RD

There is a lack of randomised controlled trials, and hence optimal treatment for IgG4-RD has not yet been established, although an international consensus guideline has been published. Even subclinical disease can lead to irreversible organ damage, but not all patients require immediate treatment. Generally speaking, treatment is tailored for individual patients, and watchful waiting may be an appropriate option for...
asymptomatic patients with mild disease involvement or following surgical debulking. When treatment is considered, glucocorticoids are used as first-line for remission induction; IgG4-RD characteristically responds promptly to therapy. Non-responders to glucocorticoid therapy are rare, although around half of IgG4-RD patients relapse during or after glucocorticoid tapering. The use of steroid-sparing agents (either upfront or sequential) has been a matter of debate, but maintenance immunosuppression is often indicated for patients with a higher risk of recurrence – especially in patients with elevated serum IgG4, IgE, and eosinophils, patients with multi-organ involvement, and patients with a history of previous relapse. Many experts now recommend rituximab, a monoclonal anti-CD20 antibody, as second-line treatment in IgG4-RD patients with recurrent or refractory disease.

IgG4 RD IN HONG KONG

Despite continued advances in the understanding of the disease and the various multinational guidelines available, few studies examined factors to predict disease severity or disease prognostication. Furthermore, local data for Hong Kong had been limited. To address this gap in knowledge, we performed an analysis of all IgG4-RD patients to elucidate the clinical features of IgG4-RD in Hong Kong (n=104) and factors predicting disease prognosis. We reported that IgG4-RD patients in Hong Kong were predominantly older (mean age 62 years), and there was a male predominance (male-to-female ratio=3:1). These findings were consistent with other reported populations. Over 95% of patients had serum IgG4 level of >135 mg/dL and an IgG4:IgG ratio of >8%. Hepatobiliary and pancreatic, and ophthalmic systems, salivary gland and lymph node(s) were the most common organ systems involved (Fig. 2). Glucocorticoids were most frequently used, while local experience with other immunomodulatory agents was limited. We also identified that pre-treatment serum IgG4 levels (β=0.347; P=0.004) were associated with salivary gland involvement and multisystem disease. The reason for this particular association remains unclear. Nonetheless, based on this finding, we recommend that salivary gland involvement should be screened in patients with IgG4-RD, especially in the presence of higher levels of serum IgG4.

CONCLUSION

IgG4-RD is a complex and relatively new systemic immune-mediated disease. Despite rapid advances, the huge disease heterogeneity sometimes makes diagnosis and treatment decisions difficult. Data from Hong Kong remains scarce, but increased physician awareness will be required for early Diagnosis and optimal management of this masquerading disease. Further studies, especially focusing on treatment strategies within the contexts of different epidemiology and patient characteristics, warrant further pursuance.

References

Systemic Vasculitis: A New Era for Giant Cell Arteritis

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INTRODUCTION

Giant cell arteritis (GCA) is classified as one of the large vessel vasculitides, according to the Chapel Hill Consensus Conference in 2012. It predominantly affects the branches of the aorta, especially the cranial arteries. It is an uncommonly recognised disease in the elderly population. The potential life-threatening complications such as irreversible loss of vision, as well as large vessel complications such as stenosis, aneurysm, and dissection of large arteries make early diagnosis and treatment of GCA crucial.

Recent advances include a better understanding of large vessel involvements, newer imaging modalities for diagnosis and the latest treatment using a biological agent targeting interleukin-6 (IL-6).

EPIDEMIOLOGY

GCA is a disease of the elderly. It rarely occurs in patients younger than 50 years of age. It is relatively rare in Asians, while it is the most common type of vasculitis in Europe and North America. The annual incidence in the prevalent regions can be as high as 17/100,000 population older than 50 years of age, while in Japan, the annual incidence is 1.47/100,000 population older than 50 years of age. Women are affected two to three times more commonly than men in Northern Europe.

PATHOPHYSIOLOGY

Genetic factors play a role in the development of the disease. HLA-DRB1*04 carrier status has been reported to have a higher risk of developing GCA. This allele is also reported more frequently in countries with a higher prevalence of GCA.

An understanding of the immunopathological pathway helps in developing novel treatments for this disease. Dendritic cells located in the adventitia-media border of large and medium arteries play a pivotal role in the pathogenesis of GCA. An unknown trigger leads to abnormal maturation of vascular dendritic cells in the large vessel wall. These antigen-presenting cells recruit T cells, the latter proliferating to T helper-one cells and T helper-17 cells. Cytokines, including interferon-gamma, interleukin (IL)-2, IL-17, IL-22, are then secreted by these activated T cells. Macrophages are then recruited, and these macrophages produce pro-inflammatory cytokines, including IL-6 and IL-1, and secrete matrix metalloproteinases, all contributing to vessel wall damages. Interferon-gamma also enhances the formation of giant cells from macrophages. All these immunopathogenetic processes lead to the characteristic features seen in the biopsied vessel wall.

CLINICAL PRESENTATION

The symptoms of GCA arise from tissue ischemia related to vasculitis of the cranial vessels. Symptoms include temporal headache and scalp tenderness due to superficial temporal artery involvement, jaw claudication due to maxillary artery involvement, tongue pain or necrosis due to lingual artery involvement. Constitutional symptoms such as fever, weight loss, anorexia are also common due to the underlying systemic inflammation. At times fever of unknown origin can be the only presentation of large-vessel GCA. New-onset headache is one of the most common presentation, while jaw claudication is the most specific. On physical examination, one must try to palpate for abnormalities over the temporal artery region, which may show tenderness, absence of pulse, or swollen temporal artery.

The most worrying complication of GCA is an irreversible loss of vision. Therefore, visual symptoms upon presentation are essential to enquire for. Around 50% of GCA patients have ocular involvement. The most common ophthalmic presentation (up to 80-90%) is anterior ischemic optic neuropathy. Patients complain of painless vision loss or amaurosis fugax. The examination will show pale or swollen optic disc but a normal retina. Central retinal artery occlusion and posterior ischemic optic neuropathy are other possible presentations. Patients may present with double vision when the blood supply of the extraocular muscles are affected.

In the absence of these classical clinical features, large vessel involvement is a previously underestimated presentation of GCA. Along with the advances in imaging techniques, including the availability of PET-CT and MRI scans, vasculitis of the thoracic or abdominal aorta is found in as high as 80% of patients with GCA. These large vessel involvements may be asymptomatic and yet, if not discovered, will bear the risk of long term complications, including stenosis, dissection, and aneurysm.

Polymyalgia rheumatica (PMR) is well recognised to be associated with GCA. Up to 50% of biopsy-proven GCA carries PMR manifestations. For PMR cases, around
20% of patients had underlying GCA\textsuperscript{10}. Therefore, one should ask about symptoms of polymyalgia rheumatica when facing a patient with suspected GCA. These symptoms include pain and stiffness in the proximal girdle, shoulder, and hip.

**HOW TO DIAGNOSIS GCA?**

The American College of Rheumatology (ACR) classification criteria (Table 1) for GCA was published in 2000\textsuperscript{11}. The symptoms included are not diagnostic criteria, and they resemble those of other confounding conditions, such as central nervous system infection.

Initial investigations should include inflammatory markers such as ESR and CRP. Normochromic normocytic anaemia and thrombocytosis may be present due to the underlying inflammation. Imaging of the brain, as well as an attempt to rule out the possibility of central nervous system infection, should be pursued. If a patient already has presented with visual symptoms, an urgent ophthalmology referral is indicated.

The gold standard for diagnosis is temporal artery biopsy. However, the sensitivity can be as low as 40\%\textsuperscript{12} due to skipping lesions, an inadequate biopsy sample, and/or prior use of steroids before a biopsy. The time required to have a biopsy report is also another reason to look for a better diagnostic tool that can give an immediate result.

Newer modalities of imaging, i.e. an ultrasound with power Doppler and/or MRI scan can offer a non-invasive way to diagnose GCA. Ultrasound of the temporal artery may show the “halo” sign, which is due to the inflamed temporal artery wall. The latest European Rheumatology guidelines on imaging for large vessel vasculitis recommends that for inpatients with classical clinical presentation and a positive ultrasound sign, temporal artery biopsy may not be necessary\textsuperscript{13}.

High-resolution MRI for the cranial arteries, black blood MR angiogram (MRA), or PET-CT scan are also useful in diagnosing GCA. MRI and MRA have the advantage over PET-CT because MRI does not use radiation.

**TREATMENT**

Irreversible vision loss in GCA is a rheumatological emergency. Prompt treatment is imperative. First-line treatment is systemic steroids. Studies have shown the benefits and effects of systemic steroids to control inflammation and to rapidly avert vision loss\textsuperscript{14}. Small studies have shown that the administration within 24 hours from the onset of symptoms may lead to better visual outcome\textsuperscript{15}. Steroid use can also prevent the contralateral eye from being involved. Systemic steroids should be given if GCA is highly suspected.

Most of the GCA patients are elderly with comorbidities that predispose them to steroid-induced side effects. Conventional steroid-sparing agents, including methotrexate, azathioprine, and mycophenolate, have been used. Small studies have proven the steroid-sparing effect of these agents\textsuperscript{6}.

The encouraging results of Tocilizumab in treating GCA patients shown in the prospective randomised controlled trial has been groundbreaking in the field of large vessel vasculitis\textsuperscript{16}. Tocilizumab is an IL-6 inhibitor. Patients in the intervention group were given 26 weeks of biweekly subcutaneous tocilizumab, together with a standard protocol of systemic steroids. Patients in the placebo group were given comparable doses of systemic steroids only. The primary outcome was the rate of sustained steroid-free remission. This study showed that patients treated with Tocilizumab demonstrated a higher rate of steroid-free remission when compared to the placebo group. The cumulative steroid dose was lower in the Tocilizumab group, demonstrating the steroid-sparing effect of the drug. Neutropenia happened in around 4% of the tocilizumab-treated group; otherwise, the rate of adverse events was similar among the two treatment groups.

Further data from the long-term extension of this landmark trial will be published soon and was presented as an abstract in the latest international Rheumatology conference\textsuperscript{17}. The initial result showed that, after two more years of follow-up, the remission rate was still higher in the Tocilizumab-treated group when compared with the placebo group. The steroid-sparing effect was also sustained.

**CONCLUSION**

With the advancements in both imaging technology and treatment, patients with GCA can now be better managed. The availability of ultrasound, MRI, and PET-CT may save patients from invasive temporal artery biopsy. Tocilizumab has recently been approved for the treatment of GCA; this new drug offers a more effective and safer alternative therapy to these patients when compared to the use of systemic steroids.
Robust and Consistent Efficacy Across PsA Domains

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**SPIRIT H2H (BIOLOGIC NAIVE): PERCENTAGE OF PATIENTS SIMULTANEOUSLY ACHIEVING**

**ACR 50 AND PASI 100 At WEEK 24, NRI**

- **Adalimumab** (N=283)
- **Taltz** (N=283)

<table>
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<th>Response Rate (%)</th>
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<th>60</th>
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† P<0.01 vs adalimumab at week 24. Onset of response was statistically significant higher as early as week 8 through to week 24.

† P<0.05 vs adalimumab at week 24.

All patients had BSA ≥3%; patients with BSA ≥10%, PASI ≥12, sPGA ≥3 followed the approved dosing for moderate to severe plaque psoriasis.

ACR50 = American College of Rheumatology response criteria with 50% improvement; BSA = body surface area; IL = interleukin; NRI = nonresponder imputation; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; sPGA = static Physician Global Assessment.


**Taltz Abbreviated Prescribing Information**

**Indications:** Plaque psoriasis - Taltz is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. **Psoriatic arthritis** - Taltz, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drug (DMARD) therapies.

**Dosage:** Plaque psoriasis - Recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks. Psoriatic arthritis - Recommended dose is 160 mg by subcutaneous injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) every 4 weeks thereafter. For psoriatic arthritis patients with concomitant moderate to severe plaque psoriasis, the recommended dosing regimen is the same as for plaque psoriasis. No data are available in children and adolescent ≤18 years and limited information in subjects ≥75 years.

**Contraindications:** Serious hypersensitivity. **Clinically important active infections. Special Precautions:** Infections, hypersensitivity, inflammatory bowel disease, immunization, Pregnancy, breastfeeding, fertility. **Adverse Reactions:** Injection site reactions, upper respiratory tract infections, tonsil infection, oropharyngeal pain, nausea.

Please see Important Safety Information in the full prescribing information.

Please see Instructions for Use included with the device.

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- Clinically significant improvement was seen as early as 1 week in a head-to-head trial of MTX-IR patients, as measured by ACR50.

ACR Scores

<table>
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<tr>
<th>PERCENTAGE OF PATIENTS (%)</th>
<th>ACR20 WEEK 12</th>
<th>ACR20 WEEK 24</th>
<th>ACR50 WEEK 12</th>
<th>ACR50 WEEK 24</th>
<th>ACR70 WEEK 12</th>
<th>ACR70 WEEK 24</th>
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<tbody>
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<td>Placebo + MTX (n = 488)</td>
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<td>5</td>
<td>10</td>
<td>11</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Olumiant 4mg + MTX (n = 487)</td>
<td>7</td>
<td>7</td>
<td>13</td>
<td>13</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Adalimumab + MTX (n = 330)</td>
<td></td>
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</tbody>
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P-value vs Placebo: ***P<0.001; **P<0.01; *P<0.05; P-value vs Adalimumab: ***P<0.001; **P<0.01; *P<0.05

OLUMIANT® (baricitinib) Abbreviated Prescribing Information

Therapeutic Indications: OLUMIANT is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. OLUMIANT may be used as monotherapy or in combination with methotrexate. Recommended dose: The recommended dose of OLUMIANT is 4 mg once daily. A dose of 2 mg once daily is appropriate for patients such as those aged ≥75 years and may be appropriate for patients with a history of chronic or recurrent infections. A dose of 2 mg once daily may also be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering. Contraindications: Known hypersensitivity to the baricitinib or any of the excipients. Pregnancy: Special precautions: Caution in patients with chronic, active or recurrent infections, monitor if infection develops; interrupt if not responding to treatment. Screen for tuberculosis, do not give if positive; treat first if latent. Avoid or interrupt OLUMIANT with abnormal blood cell levels, lipids and liver enzymes. Use with care if patients are at high risk of deep venous thrombosis or pulmonary embolism, consider VTE prophylaxis, use with TOMARO or other JAK is not recommended. Adverse reactions: The most commonly reported adverse drug reactions (ADR) occurring in ≥2% of patients treated with OLUMIANT monotherapy or in combination with conventional antirheumatics, OLUMIANT were increased LDL cholesterol (33.9%), upper respiratory tract infections (14.7%) and nasopharyngitis (6.8 %). Infections reported with OLUMIANT (treatment included herpes zoster). Drug Interactions: Concomitant use of biologic DMARDs or other JAK inhibitors has not been studied. Use of baricitinib with potent immunosuppressive medical products such as azathioprine, tacrolimus, or ciclosporin was limited in clinical studies of baricitinib, and a risk of additive immunosuppression cannot be excluded.

Full prescribing information is available upon request.


cDMARD = conventional disease-modifying antirheumatic drug; JAK = Janus kinase; MTX = methotrexate; MTX-IR = Methotrexate-Inadequate Responder

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Room 2002-28, 2/F, Chek Lap Tower, Windsor House, 334 Connaught Road, Causeway Bay, Hong Kong.
Tel: 2673 0900
Radiology Quiz

Dr Leanne Han-qing CHIN
MBBS, FRCR

An 11-year-old girl with good past health presented to Accident & Emergency Department with symptoms of right ankle swelling and pain. Multiple areas of hard swelling were also palpated at the bilateral distal thighs. Limb power, sensation, and range of motion, and overlying skin were otherwise unremarkable. There was no history of trauma. X-rays of the ankles and knees were performed.

Questions

1. What are the plain film findings?
2. What are the alternative names for this condition?
3. What is the inheritance pattern?
4. What are the important complications to be aware of?
5. What are the red flags for malignant transformation?
6. What is the next step of management?

(See P.28 for answers)
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SLE: The Management of Lupus Nephritis

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterised by multi-organ involvement and presence of antibodies to components of the cell nucleus. Clinical manifestations are heterogeneous. It frequently involves the kidneys, in up to 60% of patients. If left untreated, it may result in significant morbidity and mortality. Around 5-20% of lupus nephritis (LN) patients developed end-stage renal disease at ten years. Patients seldom report specific symptoms related to the kidneys until there is nephrotic syndrome or renal failure. The clinical renal disease is marked by more than 3+ on a dipstick, the presence of proteinuria of more than 0.5 g/24 hours, the presence of red cell casts or white cell casts, and/or elevated serum creatinine. Renal biopsy is frequently performed to delineate the specific histological features, which are stratified to different classes of lupus nephritis based on the International Society of Nephrology and Renal Pathology Society criteria (Table I).

TREATMENT GOALS OF LUPUS NEPHRITIS

The goals of treatment are to induce remission in the short term and maintain remission in the long run. The immunosuppressive therapy of LN consists of the induction phase, which takes about six months; and the maintenance phase, which takes more than three years. Induction therapy involves intensive immunosuppressive therapy in combination, and maintenance therapy involves a prolonged period of less intensive immunosuppressive therapy to prevent relapse and progression of the renal disease.

A. Class I and Class II Lupus Nephritis

Class I and Class II LN usually respond to moderate doses of corticosteroid. Choices of immunosuppressive therapy are mainly determined by the severity of the extra-renal manifestation of the disease. Azathioprine (AZA) can be used as a steroid-sparing agent. Kidney Disease Improving Global Outcome (KDIGO) guideline recommends that management should be based on concomitant extra-renal lupus manifestations if present. Corticosteroid is warranted for those with nephrotic syndrome. Immunosuppressive therapy may be necessary when the response is unsatisfactory and if relapses are frequent.

B. Class III / IV Lupus Nephritis

It is crucial to start treatment early. Delay in effective treatment implies continuous damage to nephrons, reduces renal reserve and poses negative impact on renal survival. Early aggressive treatment with high-dose corticosteroids in combination with IV cyclophosphamide (CTX) or oral mycophenolate mofetil (MMF) is recommended.

Asian Lupus Nephritis Network (ALNN) consensus recommends intravenous pulse corticosteroids at a dose of 250-1,000 mg methylprednisolone daily for three days to patients with crescentic involvement of 10% or more of the glomeruli on renal biopsy, or those with deterioration in renal function. Following the pulse corticosteroid therapy, oral prednisolone is given at lower maintenance and tapering doses. The alternative treatment is high initial dose of oral prednisolone 0.8-1 mg/kg daily. ALNN suggests the dose of the oral corticosteroids to be tapered down to a target dose of prednisolone below 20 mg daily after three months and below 10 mg daily at six months.
**Mycophenolate Mofetil vs Cyclophosphamide Induction Therapy in Class III/IV**

Ginzler EM et al. compared the efficacy and toxicity of MMF (up to 3 g/day) against National Institute of Health (NIH) IV CTX (0.5-1 g/m²) monthly for six months in 140 patients with Class III, IV or V LN. Concomitant oral prednisolone (1 mg/kg/day) was given in both groups. Of this cohort, 76% were African and Hispanic Americans, 54% had Class IV LN, and 44% were with a nephritic range of proteinuria at >3.5 g/day. At the end of six months, there were significantly more patients in MMF arm who achieved complete remission (22.5%) than in the CTX arm (5.8%). There was no difference in the rates of renal relapse, end-stage renal disease, nor death on follow-up. Pyogenic infections, alopecia, and menstrual disturbances were less common, but diarrhoea was more common in MMF arm. This study thus demonstrated evidence that MMF may be more effective and is a less toxic alternative to pulse CTX in mild to moderate LN.

No superiority of MMF over CTX was found during the induction phase of the Aspreva Lupus Management Study (ALMS). The study was a 24-week remission-induction randomised open-labeled trial comparing MMF (target dose 3 g/day) with NIH IV CTX (0.5-1 g/m² monthly for six months).

Based on the existing data, ALNN recommends MMF as the standard-of-care treatment option. For the target dosing of MMF in the induction phase, international guidelines recommend MMF up to 3 g/day. ALNN recommends 1.5-2 g daily for Asians because side effects are more common among Asians.

CTX induction may be associated with more sustained remission and more favourable renal outcome in the long term. For severe active LN with high risk of disease progression into end-stage renal disease (reduced glomerular filtration rate, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy and interstitial fibrosis), monthly pulse CTX for total six or seven doses is preferred.

**C. Pure Class V Lupus Nephritis**

Risk of renal function deterioration is much lower in pure membranous LN, and the choice of immunosuppression is mainly guided by the degree of proteinuria. Patients with a low degree of proteinuria and stable renal function can be managed with blood pressure control and ACEI or ARB. For patients with nephrotic range proteinuria or worsening proteinuria, prednisolone plus MMF (2-3 g/day) is used followed by MMF (1-2 g/day) or AZA (2 mg/kg/day) as maintenance therapy.

**D. Class VI Advanced Sclerosing Lupus Nephritis**

This class is included because it represents the last stage of lupus nephritis. Over 90% of glomeruli are sclerosed, which is the sequelae of healing following prior inflammation. Active glomerulonephritis is not usually present. Response to immunosuppressants is usually poor. This stage is characterised by gradual renal function decline and progression into end-stage renal failure.

**LONG TERM MAINTENANCE THERAPY**

Azathioprine (AZA, usually at 2 mg/kg/day) or MMF (1-2 g/day) in combination with low-dose oral corticosteroids is recommended by ACR and EULAR for maintenance therapy to consolidate LN remission and to prevent relapse. For patients treated with MMF for induction, it is preferable to continue MMF for maintenance based on data on a Chinese cohort; substituting MMF with AZA before 24 months was associated with an increased risk of renal flare. There is little evidence as to when to stop immunosuppression; EULAR recommends at least three years of MMF treatment in patients given MMF (3 g daily for 6 months) as induction therapy, then followed by lower dose of MMF (0.5-1.5 g daily) as maintenance. Asian Lupus Nephritis Network (ALNN) recommends not to reduce MMF dose below 1 g daily within the second year.

**ROLE OF CALCINEURIN INHIBITORS IN LUPUS NEPHRITIS**

Calcineurin inhibitors (CNIs) inhibit T-cell mediated immune responses and exert anti-proteinuric effect by stabilising the podocytes in the kidneys. An RCT compared tacrolimus (TAC) (0.06-0.1 mg/kg/day) with MMF (2-3 g/day) in combination with high-dose prednisolone in 150 Chinese patients with class III, IV or V active LN and suggested a comparable rate of complete renal responses (62% and 59% respectively) compared to tacrolimus (TAC) (0.06-0.1 mg/kg/day) with MMF (2-3 g/day) in combination with high-dose prednisolone (reduced glomerular filtration rate, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy and interstitial fibrosis), monthly pulse CTX for total six or seven doses is preferred.

The role of CNIs in maintenance therapy was evaluated in several studies. A study in 70 Chinese patients who received TAC or AZA for maintenance found no significant difference in the rates of renal relapses.

Using CNIs in conjunction with other immunosuppressants as a multi-target approach to achieve synergism and to facilitate a lower dosage of individual drugs has been investigated. An RCT involving 368 Chinese patients with active LN demonstrated that combination of low dose MMF (1 g/day) with TAC (4 mg/day) was superior to intravenous CTX pulses for induction of complete renal responses at 24 weeks (46% versus 26%). Withdrawal due to serious infections, herpes zoster infections, and pneumonia was more common in the multi-target group. Despite an apparent benefit in the induction phase, the role of multi-target therapy for maintenance is less clear. In the long-term extension study, the renal relapse rates were similar between patients who continued multi-target therapy and patients who received AZA after IV CTX induction.

The side effects of CNIs, including hypertension, hyperlipidemia, hirsutism, and gingival hyperplasia, are less frequently seen with TAC than with CSA. The
narrow therapeutic window, risks of nephrotoxicity and the need for therapeutic drug monitoring with TAC or CSA limit their widespread use in the treatment of LN. Voclosporin, a new analogue of CSA, has increased potency and less plasma variability than CSA and is currently under phase 3 trial after promising phase 2b trial results.

**BIOLOGICAL AGENTS FOR LUPUS NEPHRITIS**

Belimumab is a human monoclonal antibody that inhibits B-cell activating factor. It is approved in the United States and Europe to treat SLE. Rituximab (RTX) is a chimeric anti-CD20 monoclonal antibody to deplete B cells. It is currently off-label used in the treatment of LN due to controversial results among clinical studies. The LUNAR trial failed to demonstrate a superiority of RTX over MMF plus prednisolone in proliferative LN patients. In a meta-analysis of 10 studies involving over 200 RTX-treated LN patients, the pooled proportion of complete remission was 51%. Data from well-designed clinical trials on the efficacy of RTX is lacking. In the latest EULAR recommendation, RTX can be used to treat severe renal or non-renal manifestations that failed first-line immunosuppressants.

**ADJUNCTIVE MEASURES**

All LN patients should be treated with a background of hydroxychloroquine unless there is contraindication. Optimal blood pressure control is essential, and the target blood pressure should be below 130/85 mmHg. High-risk patients warrant a more aggressive control of blood pressure to below 120/80 mmHg. Proteinuria should be minimised by adding ACEI or ARB, these drugs being well-proven renoprotective agents and can retard or halt the deterioration of the renal function in chronic kidney disease. Aggressive treatment of the atherosclerosis risk factors such as the use of statins and aspirin in selected patients is essential.

**CONCLUSIONS**

The initial choices of treatment should be based on the risk stratification of individual patients. MMF should be regarded as the first-line therapy for proliferative LN. CTX should be reserved for high-risk patients such as those with crescentic glomerulonephritis, rapidly deteriorating renal function, or refractory disease. TAC can be considered an alternative to MMF for induction therapy when MMF is not tolerated or when MMF is contraindicated. Low-dose combination of MMF and TAC should be further explored in high-risk patients. Early response to immunosuppressive therapy was shown to be the best prognostic factor for good long-term renal outcome. Patients who fail to achieve a satisfactory response by six months should be switched to an alternative treatment regimen.

**References**

Impact of XELJANZ on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C should be advised to consult with clinical guidelines before starting therapy with XELJANZ. The risk of herpes zoster is increased in patients in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications. Avoid use of XELJANZ in patients with clinical evidence of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with XELJANZ. The risk of Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in patients with solid organ transplants who received XELJANZ, especially in those who received concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., ritonavir-boosted atazanavir, irtraconazole, dasatinib, bosutinib). 3. DOSAGE: Recommended dose of XELJANZ is 5 mg once daily. In patients with hepatic impairment: Recommended dose is XELJANZ 5 mg once daily. (Please refer to the full Prescribing Information for details) 8. PREGNANCY AND LACTATION: There are no adequate and well-controlled studies in pregnant women. The estimated background rate of serious infections in pregnant women is 11% in the United States. It is not known whether tofacitinib is excreted in human milk. The decision should be made whether to discontinue nursing or to discontinue the drug. 9. SIDE EFFECTS: The most common serious adverse reactions were serious infections. The most commonly reported infections with XELJANZ XR were upper respiratory tract infections, nasopharyngitis, urinary tract infections, diverticulitis and appendicitis (Please refer to the full Prescribing Information for details)  Reference: Hong Kong PI (version date/LPD date) Mar 2018  Date of preparation: May 2019; Version 13. The information contained herein is the property of Pfizer Inc. Data on file; HKPI of Xeljanz XR version13-MAR-2018
Hereditary angioedema (HAE) is a rare primary immunodeficiency disease caused by a deficiency in C1-esterase inhibitor protein (C1-INH). It is an autosomal dominant condition affecting around 1 in 50,000 individuals. Epidemiological studies vary across different geographical regions, but the prevalence of HAE in the Chinese population remains unknown. HAE is characterised by recurrent episodes of non-pruritic angioedema, which most commonly affects the extremities, face, and bowels. The most feared manifestation is laryngeal oedema, which can be complicated by life-threatening asphyxiation. Without treatment, angioedema typically lasts for 3-5 days. Psychologically, it can result in extreme anxiety and depression for patients and their families, cause significant embarrassment, limit work productivity, and pose devastating effects on the patients’ quality of life. Primarily due to the lack of awareness, HAE is often misdiagnosed or mistaken as allergy, “idiopathic” or “functional” conditions. Delay or misdiagnosis of this condition results in unnecessary investigations, intervention, and ineffective treatment. Early recognition of symptoms is paramount for early diagnosis, treatment, prevention, development of patient-centred action plans, and early family screening.

According to the World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines, there are two major forms of hereditary angioedema: HAE type I due to a C1-INH deficiency and HAE type II due to a C1-INH dysfunction. The diagnosis of HAE with a normal C1-INH level (sometimes referred to “type III”) is extremely rare and should only be contemplated in exceptional cases such as the worldwide reported cases of rare mutations in factor XII, angiopoietin-1 gene and the plasminogen genes, etc. HAE type I and II are caused by different mutations on the SERPING1 gene, which codes for C1-INH; C1-INH is a major serine protease inhibitor responsible for blocking proteases within the complement pathway, contact system and the fibrinolytic system. Bradykinin is the primary mediator for angioedema resulting in increased vascular permeability and angioedema; precursors of bradykinin, such as kallikrein and factor XII, are normally inhibited by C1-INH. In patients with HAE, a deficiency in the C1-INH will result in the dysregulation of these pathways thus precipitating bradykinin-mediated angioedema.

In clinical practice, a detailed history-taking can often help to delineate the aetiologies of angioedema (Fig. 1). More often, patients present with both wheals and angioedema, which points more towards a histamine-mediated type of angioedema – often caused by an IgE dependent or type I hypersensitivity reactions. On the contrary, bradykinin-mediated angioedema is characterised by the lack of wheals, slower progression, longer duration, lack of pruritus, and failure to respond to antihistamines and steroids. A therapeutic trial of antihistamines is sometimes warranted to guide diagnosis in cases of unclear aetiology.

Bradykinin-mediated angioedema can be further classified into hereditary and acquired causes. Foremost, we should clarify whether the patient is taking angiotensin-converting enzyme inhibitors (ACEI), and if so, the medication should be withheld to observe for the resolution of symptoms. Complete cessation of further angioedema episodes may take weeks following cessation of ACEI. Older patients without a positive family history of angioedema should prompt the possibility of acquired C1-INH deficiency, and underlying diseases should be sought, especially B-cell lymphoproliferative disease and autoimmune diseases.

Complement C4 level, C1-INH antigen levels, and C1-INH functional levels can be measured to make the diagnosis of HAE. The C4 level is a good screening test for HAE and can, in 95% of the time, be depressed while the patient is asymptomatic. The test sensitivity increases to more than 99.5% during an attack of HAE likely due to the formation of factor XII and its inhibited activation of C1r, a subunit that cleaves C4, which in turn causes cleavage of C4.

The diagnosis of type I HAE can be confirmed with a low C1-INH level. If the C4 level and C1-INH level are both normal, but a diagnosis of HAE is highly suspected, we may proceed with a C1-INH functional level, which will be low in type II HAE. In acquired C1-INH deficiency, C1-INH levels will be low, but unlike type I HAE, measurement of the complement C1q subunit will be low. Sequencing of the SERPING1 gene can support the diagnostic workup of type I and II HAE and can be relevant in cases of mosaicism.
**MANAGEMENT AND TREATMENT OF HAE**

Treatment of HAE falls into two main categories - on-demand therapy and prophylactic treatment. Patient-centred treatment plans, or action plans, should be clearly explained to patients in anticipation of an acute attack. We recommend that all patients with HAE receive on-demand therapy to stop symptoms to rapidly prevent morbidity and mortality. Treatment options for acute treatment include plasma-derived or recombinant C1-INH, icatibant, a β2 bradykinin receptor antagonist, and ecallantide, a plasma kallikrein inhibitor. They have all been shown to be efficacious against HAE attacks, and choice among these options depends on the mode of administration, cost, convenience, safety profile, and availability of the drugs. Standard treatment against histaminergic angioedema, such as adrenaline, corticosteroids, and antihistamines, are not useful in the treatment of HAE. Fresh frozen plasma should be used with caution as it may cause a paradoxical exacerbation of symptoms, likely related to the additional bradykinergic components in the pooled plasma, and should not be used if there are safer alternative medications.

It is also essential to educate patients to avoid triggers such as stress, physical trauma, alcohol, and medications, including ACEI and oestrogen-containing medications. Attenuated androgens and antifibrinolytic drugs are not shown to be efficacious for acute attacks of angioedema. If patients anticipate that there will be upcoming surgeries, or invasive medical or dental procedures, short term prophylaxis should be considered in high-risk patients. Treatment options include C1-INH replacement and attenuated androgens. Prophylaxis should be considered if the patient experiences frequent and severe attacks, and when on-demand therapy fails to improve the quality of life of HAE patients. Medications include the use of androgens, antifibrinolytics, kallikrein inhibitors, or C1-INH replacement, and use should be weighed against efficacy, costs, and side effects.

Family screening is recommended for all patients to screen for both symptomatic and asymptomatic individuals using a simple blood test checking the C4 level. In HAE type I and II, penetrance is high, but expressivity is variable, i.e., patients with diagnosed HAE may present with different symptom spectrums, severity, and frequency. Earlier diagnosis leads to more rapid recognition, avoiding unnecessary investigation and treatment. An accurate and timely diagnosis of HAE also translates to proper patient counselling and access to appropriate life-saving treatment.

**HAE IN HONG KONG**

Due to a lack of awareness and deficiency of clinical immunology services, HAE had remained largely unheard of in Hong Kong until recent years. Despite repeated hospital admissions and life-threatening attacks, many patients remained undiagnosed (some for more than 60 years!), and there are still no registered medications available for HAE locally. However, much progress in the diagnosis and management of HAE in Hong Kong has been made in recent years.

Since the establishment of the territory’s first public adult clinical immunology service at Queen Mary Hospital (QMH) in 2018, more than 35 genetically-confirmed HAE patients have now been identified. Facilities for C1-INH level, function, and genetic testing are now readily available. Prior to diagnosis, more than 20% of Hong Kong patients had a history of laryngeal attacks, and 64% of patients had been hospitalised (at least once) for acute angioedema attacks. Since 2019, all HAE patients now have access to on-demand C1-INH replacement (registered on a named-patient basis) and personalised treatment plans. Applications for novel treatments such as bradykinin and kallikrein inhibitors are also underway. Furthermore, all potentially affected family members are actively invited for counselling and screening to identify asymptomatic or undiagnosed individuals.
To promote physician awareness, an approach to diagnosing HAE has been added as a chapter in the latest edition of the Hospital Authority’s Handbook of Internal Medicine. QMH has also been recognised as an ”HAE Knowledgeable Hospital” by HAE International, and our Division has presented our findings of the first Chinese HAE registry at international conferences.

Hong Kong’s first patient support group, “hae hk” (haehk.haei.org), was also formed in 2019 to create awareness, provide education to patients/families and gain access to treatments (Fig. 2). With the combined efforts of physicians, patients, family members and volunteers, it is hoped that more undiagnosed HAE patients can be identified and access to their much-deserved treatment and higher quality of life can be established.

Fig 2: Photo of the “hae hk” patient support group (Photo from HAE Group Collection)

References


6. Craig, Timothy J. et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. Journal of Allergy and Clinical Immunology, Volume 124, Issue 4, 801 - 808


SCUBA Diving: An Imaginary “Aquaman”

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Past President, Hong Kong Society of Rheumatology

Aquaman is a superhero in a Marvel movie. Aquaman, the human-born heir to the underwater kingdom of Atlantis, goes on a quest to prevent a war between the worlds of ocean and land.

In real life, we the human beings can only go underwater with a piece of equipment called SCUBA. SCUBA stands for Self-Contained Underwater Breathing Apparatus. It has been developed to enable man to stay underwater for a certain period of time, usually around 45-60 minutes. Air is compressed into a metal tank made of either steel or aluminium. Direct breathing of compressed air will damage the lungs (barotrauma), leading to pneumothorax. Pneumothorax underwater kills.

WHAT IS SO GOOD ABOUT SCUBA DIVING?

Explore a New World

The ocean is a new world to land animals like us. Your eyes will access a whole new dimension filled with marine life and biodiversity. Bright coral reefs, flashy invertebrates, curious marine mammals like whales and an unbelievable array of colourful fishes. Diving brings you closer to nature, and it always gives you surprises.

Weightlessness

There are two ways to go weightlessness on earth. The first but expensive way is flying with the Zero-G plane, which is a modified Boeing 727 plane. You can experience zero gravity, flip and soar inside this special plane. The second choice is to go SCUBA diving. The feeling of weightlessness kicks in when one is descending into the deep blue sea. You would feel like you are flying in the sea, another dimension on earth. All the city noises are gone; you can only hear your breathing sound. All the chaos, troubles, and worries of everyday life vanish in those minutes underwater. The experience is tranquillising and addictive. Some divers would go straight into Zen mode.

Socialising and Making New Friends

When we are kids, we make new friends all the time. You meet people in a class, in church and even in sports competitions. When we grow up, meeting new people at times brings apprehension for some people. The buddy system in SCUBA diving provides a platform for making new friends or even having a buddy for life. Divers with different cultural backgrounds can share their own sea stories. There’s always something interesting to share, such as finning over fantastic coral reef, watching big schools of fishes, drifting over the edges of dramatic drop-offs, diving in ancient wrecks, or exploring the incredible underwater landscape. But perhaps the best thing of all is sharing the adventure with like-minded friends, family, and buddies.

Redefine Your Limits

From time to time, we lose sight of a bigger picture of ourselves. We get caught up with our busy schedules, running errands, family stuff, etc. Sometimes, we forget we can live our lives outside these daily routines.

HOW CAN THE COMPRESSED AIR BE MADE SAFE TO BREATHE?

The purpose of a SCUBA diving regulator is to reduce the high-pressure in the air tank to a breathable ambient pressure on demand. Let’s begin with some terminology and concepts.

First Stage: The first stage of a SCUBA diving regulator is the part of the regulator that attaches to the tank valve.

Second Stage: The second stage of a diving regulator is the part that the diver puts into his mouth.

The air inside a tank is compressed to a very high pressure to increase the air supply for a diver. A full SCUBA tank is often pressurised to 3,000 psi or 200 bars. Air pressure at sea level is 1 bar. The pressure surrounding the diver changes according to the depth of water. The genius design of the diving regulator is that the second stage automatically adjusts to the diver’s depth and creates ambient pressure. This smart design allows man to enjoy and explore the wonders of the underwater world.

CERTIFICATION OF A SCUBA DIVER

A diver is certified when a person has completed a course of training as required by the agency issuing the card. The certificate card represents a defined level of skill and knowledge in underwater diving. The origin of the certification comes from a tragic accident in 1952 after two divers died while using university-owned equipment. Recreational certifications are issued by various agencies, such as NAUI and PADI.
Sometimes we give too many excuses to ourselves, “I am not capable of,” “I don’t have time,” “do it later,” “I am afraid of trying new things,” “I don’t think I am good at,” or even “I am too old for this”. SCUBA diving can energise you by taking you out of your comfort zone. It provides you with a sense of accomplishment once you have mastered the skill. The deep-water exploration stretches your unthinkable area. Each dive is a new challenge that reshapes your limits.

**Increase Your Confidence and Self-esteem**

A return to the water after a break can give the diver a pre-dive apprehension. In order to tackle all the challenges underwater, a well-planned and well-executed dive is imperative to all divers. Keeping fit is an excellent way to improve confidence in dealing with any psychological or physical stress one may face during diving. Aerobic exercise program with regular cardiovascular boost-up training is of paramount importance. Having a good physique increases your self-esteem and confidence. This confidence can extrapolate your confidence in dealing with adversities in work and life.

In a nutshell, SCUBA diving brings many good things to your life. It is never too late to start reinventing yourself!
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Answers to Radiology Quiz

Answers:

1. Multiple bony outgrowths of sessile and pedunculated configurations are seen arising from metaphyseal regions of the long bones. They project away from the epiphysis. Broadening of the metaphysis, especially at right distal tibia is evident with mild ankle deformity. There are no aggressive bony features such as cortical destruction or large soft tissue component. No pathological fractures are evident.

   - Hereditary multiple exostoses
   - Diaphyseal aclasis (due to association with broadening of the shaft at the end of long bones)
   - Osteochondromatosis

2. Autosomal dominant inheritance, with incomplete penetration in females.

3. Neurovascular impingement
   - Pathological fracture (especially pedunculated exostosis)
   - Bursitis
   - Deformity, limb-length discrepancy
   - Malignant transformation

4. The mnemonic “GLAD PAST” is useful for memorising features of malignant (sarcomatous) transformation:
   - G: Growth after skeletal maturity
   - L: Lucency (new)
   - A: Additional scintigraphic activity
   - D: Destruction (bony cortical)
   - P: Pain after puberty
   - A: and
   - S: Soft tissue mass
   - T: Thickened cartilage cap >1.5cm (detected on MRI)

5. No further active management is required as osteochondromas on its own are benign
   - Regular follow-up is recommended to observe for complications as mentioned above, especially malignant transformation (with reported rates as high as 25%).

Dr Leanne Han-qing CHIN
MBBS, FRCR
Shining Light on an Overlooked Disease

GOUT

Maintenance of suA<6.0 mg/dl

leads to benefit in preservation of renal function.

*From a post-hoc analysis of the FOCUS trial, maintenance of suA at <6.0mg/dL for 5 years led to overall stabilization of renal function as reflected in mean eGFR and sCr.

References:
The ONE & ONLY approved biologic for SLE treatment
New autoinjector for your patients

When standard therapy is not enough, why not choose BENLYSTA?

- Superior disease activity reduction at week 52
- Reduced risk of severe SLE flares over 52 weeks
- Reduction in cumulative steroid dose over weeks 52
- Rate of adverse events were similar between BENLYSTA and placebo
- Emerging evidence on organ damage progression
- Fewer patients experienced renal flares vs standard therapy alone in patients with baseline proteinuria >0.5g/24hrs

References:

BENLYSTA is a human IgG1 monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS, also known as B cell activating factor or BAFF) and is approved for the treatment of adults with active systemic lupus erythematosus (SLE) in combination with a standard of care (SOC) immunosuppressant(s). BENLYSTA is indicated for the treatment of adults with active SLE who have received one or more disease-modifying antirheumatic drugs (DMARDs), and for whom there is a lack of adequate response to SOC therapy. This indication is approved in the U.S. and EU. It is not known whether belimumab will significantly delay the progression of lupus nephritis, a frequent complication of SLE. However, a decrease in proteinuria was seen in some patients in clinical studies, and belimumab has been shown to increase global health scores and reduce the frequency of flares in the clinical trial data. Studies evaluating the role of belimumab in preventing renal flares are ongoing in patients with lupus nephritis.

Physicians should exercise caution when considering the use of BENLYSTA in patients with chronic infections or a history of recurrent infection. Live vaccines should not be given for 30 days before, during, or immediately after treatment with BENLYSTA. Patients should be monitored for any of these new or worsening symptoms or signs suggestive of progressive multisystem vasculitis/lymphocytosis and if any sign or symptom is severe or persistent, evaluation should be performed as clinically indicated. Patients with active SLE should be monitored closely and careful consideration given to interrupting immunosuppressant therapy including belimumab until the infection is resolved. Patients should be monitored for antinuclear antibodies titers. Patients should be monitored for renal function and creatinine levels. Patients should be monitored for sensitivity to any of the excipients of belimumab. Patients should be monitored for hypersensitivity reactions. Patients should be monitored for long-term effects of belimumab on malignancy rates or second malignancy risk. Physicians should exercise caution when considering the use of belimumab in patients with severe or chronic infections or a history of recurrent infection. Physicians who develop clinical suspicion while undertaking treatment with BENLYSTA should be referred to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until the infection is resolved. Physicians should exercise caution when considering the use of belimumab in patients with severe or chronic infections or a history of recurrent infection. Physicians who develop clinical suspicion while undertaking treatment with BENLYSTA should be referred to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until the infection is resolved. Physicians should exercise caution when considering the use of belimumab in patients with severe or chronic infections or a history of recurrent infection. Physicians who develop clinical suspicion while undertaking treatment with BENLYSTA should be referred to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until the infection is resolved. Physicians should exercise caution when considering the use of belimumab in patients with severe or chronic infections or a history of recurrent infection. Physicians who develop clinical suspicion while undertaking treatment with BENLYSTA should be referred to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until the infection is resolved. Physicians should exercise caution when considering the use of belimumab in patients with severe or chronic infections or a history of recurrent infection. Physicians who develop clinical suspicion while undertaking treatment with BENLYSTA should be referred to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until the infection is resolved.

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