Crusted cutaneous lesions, what is your diagnosis?

DOACs, health benefits and patient preference
- Phosphate replacement in the ICU
- MAS with lung involvement complicating AOSD
- Central diabetes insipidus: beware of LCH!
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To promote and to enhance clinical knowledge by publishing editorials, original articles, reviews, papers regarding
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In the current issue of the journal, Wang et al. present a patient with adult-onset Still’s disease suffering from macrophage activation syndrome (MAS) with pulmonary involvement.

Adult-onset Still’s disease is a rare acquired autoinflammatory disorder with similar presentation to the present-day systemic juvenile idiopathic arthritis (sJIA). Some regard it a continuum of a single disease entity. The frequently-used term ‘periodic fever syndrome’ is not justified as fever and is not always part of the presentation. Incidence is approximately 0.16 per 100,000 individuals with an equal distribution between men and women. The clinical course can be divided in a mono-phasic, intermittent and chronic disease pattern and severity is variable. Skin and joint disease, lymphadenopathy and spleen and liver involvement are common. MAS is regarded the most serious presentation with high mortality despite treatment. Markedly elevated ferritin levels are often a clue to diagnosis.

Treatment is aimed at inhibiting pro-inflammatory signs and symptoms, and thereby preventing organ damage and life-threatening complications. Yet, optimal treatment for this disease remains to be elucidated as large clinical trials are lacking. For mild disease with mainly joint involvement, nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed. Corticosteroids are given to patients with more aggressive disease. In severe refractory disease, it has been common use to start treatment with disease-modifying antirheumatic drugs (DMARDs). Wang et al. successfully treated the patient with cyclophosphamide after corticosteroids alone failed to control disease activity. She fully recovered. In their discussion, they suggest that blocking pro-inflammatory cytokines would have been an attractive treatment option for this patient; pro-inflammatory cytokines such as IL-1, IL-6 and IL-18 play a prominent role in the pathogenesis of sJIA and adult-onset Still’s disease, and high-dose corticosteroids and cyclophosphamide have considerable side effects, especially in young patients.

Biologics blocking IL-1 and IL-6 are available and studies have demonstrated very effective control of disease activity with acceptable side effects. Also recently, a study has been published showing the effect of blocking IL-18. Perhaps in the near future, there may also be a role for blocking interferon gamma.

There is discussion whether cytokine blocking should be administered earlier in the disease process to avoid side effects of other drugs such as high-dose corticosteroids. Unfortunately, medication costs still hamper this. In addition, quality of life during and after treatment should equally be weighed while deciding what treatment is best for patients.

REFERENCES

REVIEW

Trends in direct oral anticoagulant (DOAC) use: health benefits and patient preference

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ABSTRACT

In 2012, the Dutch Health Council published a report addressing barriers for an early and broad introduction of direct oral anticoagulants (DOACs). The report raised concerns about the lack of an antidote, adherence, lack of monitoring in the case of overdose and the increased budget impact at DOAC introduction. In the past decade, international studies have shown that DOACs can provide healthcare benefits for a large number of patients. This has led to an increase in the prescription of DOACs, as they are an effective and user-friendly alternative to vitamin K antagonists (VKAs). Unlike VKAs, DOACs do not need monitoring of the international normalized ratio due to more predictable pharmacokinetics. However, the number of prescriptions of DOACs in the Netherlands is still lagging, compared to other European countries. This article highlights the potential health gains in the Netherlands if the use of DOACs were to increase, based on current international experience.

KEY WORDS

DOAC, NOAC, health benefits, patient preferences, VKA, coumarins

BACKGROUND

Various international studies have shown that direct oral anticoagulants (DOACs) can provide healthcare benefits for a large number of patients.13 In the Netherlands, DOACs are available for the treatment of venous thromboembolism (VTE), stroke prevention in non-valvular atrial fibrillation (NVAF) and as a short-term prophylaxis of VTE after total hip and knee replacement.14 Dabigatran (Pradaxa®), rivaroxaban (Xarelto®), apixaban (Eliquis®) and edoxaban (Lixiana®) are currently registered in the Netherlands and are approved for application in NVAF and VTE patients. Phase 3 clinical trials have shown that DOACs are at least as effective as vitamin K antagonists (VKAs).5-13 DOACs also have significantly better outcomes with regard to intracranial bleeding.14 VKAs require international normalized ratio (INR) monitoring due to unpredictable pharmacokinetics, and are also known for many food and drug interactions. DOACs, on the other hand, have a more direct inhibiting mechanism on the coagulation factors Xa (apixaban, edoxaban and rivaroxaban) or IIa (dabigatran), making INR monitoring unnecessary.4 This, together with fewer food and drug interactions make DOACs a more user-friendly treatment option.

Since the introduction of DOACs, the prescription numbers in the Netherlands are lower when compared to most other European Union (EU) countries. This article highlights the potential health gains in the Netherlands if the use of DOACs were to increase, based on the current international experience with DOACs. Therefore, we will first provide an overview of trends, including scientific, real-life and pharmacoeconomic data on DOAC use for the indication NVAF in the Netherlands.
introduction of a new class of drugs, DOACs,\textsuperscript{15} and recommended careful monitoring and suggested registration of bleeding and thrombotic complications. The report also mentioned three barriers for early and broad introduction of DOACs in the Netherlands: 1) lack of an antidote, 2) doubts about adherence and lack of monitoring in cases of overdose, and 3) increased budget impact at DOAC introduction.\textsuperscript{15} The Health Council’s advice resulted in conservative prescription dispensation and slow increase in use of DOACs. Furthermore – although never mentioned explicitly – the strong established position of regional and hospital-based thrombosis service centers may have played an influential role in the Health Council’s advice. In the Netherlands, we have a unique, very well-organized and specialized Thrombosis Service,\textsuperscript{16} which monitors all patients using VKAs, including their international normalized ratio (INR), which is regularly measured with subsequent dose adjustment. With the introduction of DOACs, these centers may become redundant, causing unemployment.

Health benefits and patient preference

Clinical research has shown that anticoagulant treatment with DOACs is at least equivalent to standard therapy with VKAs in terms of effectiveness and adverse events,\textsuperscript{13} therefore, DOACs may be a practical and user-friendly alternative treatment for a large group of patients.\textsuperscript{17,18} Clinical data from 50 trials included in a meta-analysis have illustrated that treatment with DOACs led to significantly better overall outcomes in hemorrhagic side effects compared to VKA treatment.\textsuperscript{19} A 2015 study by Boom et al. demonstrated that Dutch patients prefer DOAC over VKA treatment, primarily because of a lower risk of hemorrhagic events and non-requrement for INR monitoring.\textsuperscript{20,21} Despite the benefits of DOAC treatment, it might not be the best choice for every patient. There are limited data concerning vulnerable elderly patients (75+ years of age) and patients with impaired renal function; thus, clinicians should prescribe DOACs for these specific populations with caution.\textsuperscript{21}

Health benefits are usually expressed in Quality-Adjusted Life Years (QALYs) gained, where 1 is equal to perfect health and 0 equals death. Using quality of life outcomes from a study addressing stroke prevention in NVAF patients from a Dutch perspective, we calculated a weighted average health benefit of 0.276 QALYs per patient in favor of DOACs (apixaban, dabigatran, rivaroxaban) compared to VKA therapy.\textsuperscript{22} The weighted average was calculated by the number of QALYs per patient gained, adjusted by the distribution of DOAC use (apixaban, dabigatran and rivaroxaban) in the Netherlands in 2014.\textsuperscript{14} Several studies performed by the University of Groningen reported comparable cost-effectiveness between DOACs (dabigatran, rivaroxaban and apixaban) and VKA acenocoumarol in VTE and NVAF patients.\textsuperscript{24-27} All studies associate DOAC use with potential health benefits, especially in patients with characteristics comparable to the different NVAF and VTE trial populations; elderly patients with impaired renal function should still be treated with caution.

DOAC use: A comparison of the Netherlands to other EU countries

For our current analysis, we compared the Netherlands to Belgium and Germany because of their similar healthcare systems and economies. In 2010, the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF Registry) was established to gain insight into DOAC use for NVAF in different European countries.\textsuperscript{28} Comparing Dutch prescription rates to other Western European countries shows a slower uptake of DOAC use in the Netherlands. From 2010 to 2014, the number of DOAC anticoagulated German and Belgian patients in increased from 4.3% and 50.0% to 24.8% and 57.0%, respectively.\textsuperscript{29} Dabigatran treatment for the indication NVAF received approval in Germany in August 2011; this occurred more than a year later in October 2012 in the Netherlands and Belgium, which could explain its higher use in Germany.\textsuperscript{28} Another reason may be that general practitioners (GPs) in the Netherlands strictly adhere to guidelines, and generally only start prescribing a new drug when it is endorsed by the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG). For DOACs, this did not occur until late 2016,\textsuperscript{29} and this ‘waiting’ approach may have further delayed DOAC use.

Potential health gains in the Netherlands

If we assume that the use of DOACs increases to levels comparable to Belgium or Germany, we can estimate possible health gains in Quality Adjusted Life Years (QALYs). We calculated these QALYs for the year 2014 since we based our calculations on prescription numbers in the GARFIELD-AF study, which included numbers updated to 2014. According to the 2014 annual medical report of the Federation of Dutch Thrombosis Service (Federatie van Nederlandse Thrombosdiensten), there were a total of 307,067 VKA-treated NVAF patients in the Netherlands.\textsuperscript{30} Based on ATC codes (internationally accepted Anatomical Chemical Classification), the number of users of apixaban, dabigatran and rivaroxaban in the year 2014 could be identified.\textsuperscript{31} The potential health gains were calculated by multiplying the aforementioned weighted average of incremental QALYs for NVAF patients when switched from VKA to a DOAC, and we calculated that the number of patients that could have been on a DOAC when using German or Belgium prescription levels.\textsuperscript{32,33} This number of patients was based on the percentage of NVAF patients on DOACs in Germany and

\textsuperscript{de Jong et al. DOACs, health benefits and patient preference.}
Belgium multiplied by the Dutch NVAF population in 2014. With these calculations, we conclude that an increase in DOACs prescriptions to German or Belgian levels would have led to 50,242 (+14.3%) or 163,376 (+40.5%) additional DOAC users, corresponding with 13,876 to 45,121 QALYs gained.

In addition to the increase in quality of life, DOAC therapy is associated with higher costs compared to VKA. The Health Council of the Netherlands reported an incremental cost-effectiveness ratio (ICER) of €12,000/QALY for the introduction of DOACs. According to this report, the additional costs related to the possible health gains would have been €167 to €541 million. Of note, ICERs are calculated over a patient’s lifetime and QALY gains and accordingly, costs are not reached within this one year.

Current situation
Recent Dutch data from the Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetalien, SFK) showed a 75% increase of DOAC prescriptions in the year 2016 compared to the year before (figure 1). The number of patients on VKAs has declined from 465,000 to 440,000 users (-9%) between the years 2015 and 2016. Based on these statistics, we calculated that by the end of 2016, approximately 26% of all anticoagulated patients in the Netherlands received a DOAC. This might be explained by the update of the European Society of Cardiology (ESC) for NVAF and American College of Chest Physicians CHEST Guidelines for VTE in 2016, in which new patients are recommended to start with a DOAC. In the same year, the Dutch Association for Internal Medicine (Nederlandse Internisten Vereniging) published their new thromboprophylaxis guideline, which positions DOACs over VKA for the treatment of VTE. Moreover, the NHG Guidelines stated in 2016 that VKAs are equal to DOACs. Although guidelines are more positive towards DOAC treatment, there are still some unaddressed clinical issues that need to be clarified. With regard to these issues, a branch of the ESC, the European Heart Rhythm Association (EHRA) published – at the request of clinicians – a practical guide with answers to specific clinical questions on the use of DOACs in patients with NVAF for example, how to deal with DOACs in the perioperative period. An article by Camm et al. discusses the implementation of these ESC guidelines in practice, which might also help clinicians optimize DOAC treatment strategies. In addition to guideline adaption, there are more explanations for the increased prescription numbers, for example the positive results of real world data and studies on effectiveness, safety and adherence in more specific populations such as the elderly and patients with impaired renal function. Recently, the DUTCH-AF registry was established to provide more information on these specific populations in the Netherlands. The project is an intensive collaboration between cardiologists,
GPs, internists and neurologists, and aims to provide insight into daily practice DOAC use in atrial fibrillation (AF) patients. Information on effectiveness, safety and adherence in specific patient populations can be used to optimize the anticoagulation treatment in AF patients. Furthermore, the development of antidotes and more experience and guidance on how to deal with DOACs in specific clinical situations for example, different types of surgery and interventions, may have contributed to increased prescription numbers. The antidote for dabigatran, idarucizumab, has recently been introduced on the market, while andexanet alfa, used to reverse factor Xa inhibition (by rivaroxaban, apixaban, edoxaban or enoxaparin), is currently being studied in a phase 3b/4 clinical trial, The Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors (ANNEXA-4).

CONCLUSION

DOACs are now well-established alternatives to VKA for anticoagulation treatment in NVAF and VTE patients. However, the use of DOACs in the Netherlands is relatively low compared to various neighboring countries such as Germany and Belgium. Currently, prescription numbers are increasing, but more supportive data on real world effectiveness, safety and adherence in more specific patient populations is needed to help further increase this number. We calculated that increasing the use of DOACs in the Netherlands up to 2014 German and Belgian levels could have led up to 50,242 (+ 14.3%) or 163,376 (+ 46.5%) additional DOAC users, corresponding with 13,876 to 45,121 QALYs gained, respectively.

DISCLOSURES

This study was funded by Bayer. De Jong, Koops, Gout-Zwart, Beinema and Brouwers have no conflicts of interest with relation to the subject. Postma has received educational and research grants from Boehringer Ingelheim, Bayer and Bristol-Myers Squibb. Hemels received speakers’ fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer and Daiichi Sankyo.

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de Jong et al. DOACs, health benefits and patient preference.
Hypereosinophilia: a diagnostic challenge

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ABSTRACT

Hypereosinophilia encompasses a broad differential diagnosis of atopy/allergic reactions, drug reactions, parasitic infections and paraneoplastic syndromes. Although mostly of limited clinical significance, hypereosinophilia can also be related to hematological malignancies. One has to be aware of the potential for secondary organ damage for example, in the case of hypereosinophilic syndrome. We present three cases with different underlying mechanisms of hypereosinophilia with a brief overview of causes, diagnostic work-up and treatment options.

KEY WORDS

Hypereosinophilia, parasitic infections, strongyloidiasis, allergy, hypereosinophilic syndrome, hypereosinophilia of unknown significance, hematological malignancy, chronic eosinophilic leukemia, imatinib, mepolizumab, corticosteroids, ivermectin

CASE HISTORIES

Patient A
A 29-year-old man with an unremarkable past medical history was clinically observed with fever (40°C) and myalgia two weeks after his return from Thailand. He suffered from nausea and mild abdominal pain. During his stay he had a short-lived episode of diarrhea. On physical examination, he had a temperature of 38.6°C and an erythematous maculopapular rash on his right flank and buttocks. Laboratory examination was unremarkable apart from an increased C-reactive protein (CRP) level (223 mg/l). Differential diagnosis included Rickettsiosis (scrub typhus), Salmonella typhi and Melioidosis (Burkholderia pseudomallei). Malaria was excluded. Dengue, Chikungunya and Leptospirosis were less likely based on their shorter incubation periods. During his admission, he was treated with doxycycline and discharged after four days. On follow-up three weeks later, CRP-level had normalized, but a significant leucocytosis of 24 x 10^9/l had developed with 71% eosinophilia; his absolute eosinophil count was 17 x 10^9/l. Serological examination and a Triple Faeces Test (TFT) confirmed an infestation with Strongyloides stercoralis. The patient was treated with ivermectin (200 µg/kg) and made a full recovery. His absolute eosinophil count dropped to 0.78 x 10^9/l. Most likely, the patient was infected while walking barefoot along the shores of the River Kwai. These dermatological phenomena due to strongyloides is known as larva currens.

Patient B
A previously healthy 62-year-old female presented with diplopia, progressive gait problems and numbness and tingling of hands and feet. She reported a recent flu-like episode with persistent complaints of weight loss and discomfort between the shoulder blades. Physical examination was unremarkable apart from multiple small cervical lymph nodes. Laboratory examinations showed an erythrocyte sedimentation rate (ESR) of 72 mm/hour, leukocytosis of 14 x 10^9/l and CRP of 71 mg/l. Leukocyte differentiation showed 21% eosinophils, with no increase in progenitor cells or basophils. The absolute eosinophil count was 4.4 x 10^9/l. Differential diagnosis included paraneoplastic syndrome associated with underlying malignancy or vasculitis. Guillain-Barre syndrome was found to be unlikely. Full body computerized tomography (CT) scan showed no primary tumor or distant metastasis and magnetic resonance imaging (MRI) showed no intracranial abnormalities or signs of vasculitis. Spinal
fluid was normal. Immunological assays to autoantibodies antinuclear antibody and antineutrophil cytoplasmic antibody (ANA/ANCA) were negative and therefore, autoimmune disease was unlikely. Mastocytosis was also unlikely due to normal tryptase levels. During admission, a progressive neurologic condition evolved, which was characterized by neuropathy, gait function disorders, facial paralysis and ptosis. Based on the progressive course of the disease, in combination with hypereosinophilia, a hypereosinophilic syndrome (HES) was suspected. Bone marrow examination revealed an eosinophil count of ≥ 20% with no increase in blasts. Bone marrow biopsy showed neither morphological aberrations, nor increase of mast cells. Molecular tests were unremarkable (no C-KIT, BCR-ABL, JAK2 or CALR mutations) and fluorescence in situ hybridization (FISH) did not detect the FIP1L1-PDGFRA fusion gene. Additional cytogenetic tests ultimately revealed a 20q-deletion, as observed in patients with chronic eosinophilic leukaemia (CEL). The patient was treated with high-dose intravenous prednisolone of 60 mg, once daily. Because of the severity of symptoms, she was concomitantly treated with interferon-alpha. She slowly recovered and during several outpatient visits, her eosinophil count eventually normalized.

**Patient C**

A man, aged 23, known with type I diabetes mellitus presented to the emergency department with acute diarrhea and vomiting. Apart from mild discomfort in the right lower quadrant of his abdomen, physical examination on admission was unremarkable. Laboratory examination showed a leucocytosis of 14 x 10^9/l. Ultrasound and subsequent CT scan showed ascites with diffuse bowel thickening of his ascending and transverse colon. Follow-up laboratory tests showed the development of a significant eosinophilia with an eosinophil percentage of 48% and an absolute eosinophil count of 7.2 x 10^9. Detailed history regarding allergies, medication and travel history was inconclusive. Stool sample cultures for pathogens remained inconclusive. Fluid was normal. Immunological assays to autoantibodies antinuclear antibody and antineutrophil cytoplasmic antibody (ANA/ANCA) were negative and therefore, autoimmune disease was unlikely. Mastocytosis was also unlikely due to normal tryptase levels. During admission, a progressive neurologic condition evolved, which was characterized by neuropathy, gait function disorders, facial paralysis and ptosis. Based on the progressive course of the disease, in combination with hypereosinophilia, a hypereosinophilic syndrome (HES) was suspected. Bone marrow examination revealed an eosinophil count of ≥ 20% with no increase in blasts. Bone marrow biopsy showed neither morphological aberrations, nor increase of mast cells. Molecular tests were unremarkable (no C-KIT, BCR-ABL, JAK2 or CALR mutations) and fluorescence in situ hybridization (FISH) did not detect the FIP1L1-PDGFRA fusion gene. Additional cytogenetic tests ultimately revealed a 20q-deletion, as observed in patients with chronic eosinophilic leukaemia (CEL). The patient was treated with high-dose intravenous prednisolone of 60 mg, once daily. Because of the severity of symptoms, she was concomitantly treated with interferon-alpha. She slowly recovered and during several outpatient visits, her eosinophil count eventually normalized.

### Table 1. Criteria and definitions

<table>
<thead>
<tr>
<th>Hypereosinophilia (HE)</th>
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<tbody>
<tr>
<td>Absolute eosinophil count &gt; 1.5 x 10^9/l on at least two occasions with an interval of ≥ 1 month and/or histologically proven eosinophilia in tissue defined as:</td>
</tr>
<tr>
<td>1. Bone marrow aspiration with ≥ 20% eosinophils and/or</td>
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<tr>
<td>2. Histologically proven tissue infiltration and/or</td>
</tr>
<tr>
<td>3. Deposition of eosinophil-granule proteins</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Hypereosinophilic syndrome (HES)</th>
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<tbody>
<tr>
<td>1. Existence of hypereosinophilia as defined above and</td>
</tr>
<tr>
<td>2. Eosinophil-mediated organ dysfunction and/or damage and</td>
</tr>
<tr>
<td>3. No other identifiable etiology for eosinophilia</td>
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### Background

Normal peripheral eosinophil counts vary between 0.04-0.60 x 10^9/l. Peripheral blood eosinophilia can be divided into mild (0.5-1.5 x 10^9/l), moderate (1.5-5 x 10^9/l), and severe (> 5 x 10^9/l). The term hypereosinophilia (HE), as used in this manuscript, is defined as an absolute eosinophil count of > 1.5 x 10^9/l measured on at least two occasions with an interval of ≥ one month and/or histologically proven tissue infiltration by eosinophils (table 1). Milder eosinophilia can be caused by countless conditions, infectious, autoimmune or cryptogenic notably, HIV infection, granulomatous disorders, polyarthritis nodosa and primary biliary cirrhosis. Furthermore, the term hypereosinophilic syndrome (HES) is defined as the existence of HE in combination with eosinophil-mediated organ damage. The term HES cannot be used if the clinical symptoms and organ involvement have a clear identifiable etiology. The exact incidence and prevalence of HE and HES remain uncertain. The age-adjusted incidence rate is estimated 0.036 per 100,000 individuals per year.\(^1-3\)

### Pathophysiology

Eosinophils are leucocytes originating from CD34+ hematopoietic precursor cells in the bone marrow. The most important growth factors for eosinophils are interleukin 3 (IL-3), IL-5 and granulocyte-macrophage colony-stimulating factor. They not only trigger growth but also activate normal and neoplastic eosinophils.\(^4,5\) There are two pathophysiological mechanisms that can contribute to the development of HE. First, overproduction of eosinophilopoietic cytokines can cause an increase in differentiation and massive proliferation. Subsequently, there is an increase in migration, adhesion, activation and survival of the eosinophils.\(^4,6\) The second mechanism includes rapid monoclonal proliferation
of eosinophils from myeloid progenitor cells caused by gene rearrangements of oncogenic tyrosine kinase receptors, such as PDGFRα, PDGFRβ or FGFR1 (table 2). Fusion of the PCM1-JAK2 gene was added as a provisional entity in 2016.

These mutated receptors induce constitutive tyrosine kinase activation, resulting in uncontrolled stimulation of eosinophilic progenitor cells. CEI is often caused by deletion of 4q12, resulting in the FIP1L1-PDGFRA fusion gene. Reactive hypereosinophilia can thus develop due to overproduction of cytokines and growth factors, or be the result of clonal eosinophilia caused by myeloproliferative disorders.

In the setting of persistent and massive activation, eosinophils can invade target organs and release their toxic mediators. These eosinophil-derived substances may cause profound changes in the microenvironment and can lead to resultant endomyocardial fibrosis, thrombosis, cutaneous symptoms, peripheral or central neuropathy (with chronic of recurrent neurologic deficit) and other less common organ manifestations.

Etiology

Many conditions are associated with HE and HES, and can be divided into several subgroups in which reactive hypereosinophilia occurs most frequently (table 3). Worldwide, parasitic infections are the major cause of HE (table 4), with the most prevalent being hookworms, ascariasis and filariasis infections, followed by schistosomiasis and strongyloidiasis. In areas where there is little exposure to parasites, allergies and medication-induced HE are the leading cause. Solid tumors and autoimmune disorders occur less frequently. Finally, only a small proportion is caused by the remaining other syndromes shown in table 3, unfortunately, the exact relation between these syndromes and the development of HE is often obscure.

Table 2. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ABPA</td>
<td>Allergic bronchopulmonary aspergillosis</td>
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<tr>
<td>AEP</td>
<td>Acute eosinophilic pneumonia</td>
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<tr>
<td>ALL</td>
<td>Acute lymphatic leukemia</td>
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<td>ANA</td>
<td>Antinuclear antibodies</td>
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<tr>
<td>ANCA</td>
<td>Antineutrophil cytoplasmic antibodies</td>
</tr>
<tr>
<td>BCR-ABL</td>
<td>Breakpoint cluster region - Abelson</td>
</tr>
<tr>
<td>CBFb</td>
<td>Core binding factor complex</td>
</tr>
<tr>
<td>CEP</td>
<td>Chronic eosinophilic pneumonias</td>
</tr>
<tr>
<td>CML</td>
<td>Chronic myeloid leukemia</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CSS</td>
<td>Churg-Strauss syndrome</td>
</tr>
<tr>
<td>CT</td>
<td>Computer tomography</td>
</tr>
<tr>
<td>EMS</td>
<td>Eosinophilia-myalgia syndrome</td>
</tr>
<tr>
<td>FGFR1</td>
<td>Fibroblast growth factor receptor-1</td>
</tr>
<tr>
<td>FIP1L1-PDGFRA</td>
<td>FIP1-like-1-platelet-derived growth factor receptor-alpha</td>
</tr>
<tr>
<td>FISH</td>
<td>Fluorescent in situ hybridization</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Granulocyte-macrophage colony-stimulating factor</td>
</tr>
<tr>
<td>HE</td>
<td>Hypereosinophilia</td>
</tr>
<tr>
<td>HEUS</td>
<td>Hypereosinophilia of unknown significance</td>
</tr>
<tr>
<td>NHL</td>
<td>Non-hodgkin lymphoma</td>
</tr>
<tr>
<td>PCM1-JAK2</td>
<td>Pericentriolar material 1-Janus kinase2</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PDGFRα</td>
<td>Platelet-derived growth factor receptor alpha</td>
</tr>
<tr>
<td>PDGFRβ</td>
<td>Platelet-derived growth factor receptor beta</td>
</tr>
<tr>
<td>PMN</td>
<td>Polymorphonuclear neutrophils</td>
</tr>
<tr>
<td>SM</td>
<td>Systemic mastocytosis</td>
</tr>
<tr>
<td>TFT</td>
<td>Triple faeces test</td>
</tr>
</tbody>
</table>

Table 3. Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive/secondary HE and HES</td>
</tr>
<tr>
<td>Parasitic infections</td>
</tr>
<tr>
<td>Allergies/atopy, ABPA</td>
</tr>
<tr>
<td>Medication-induced</td>
</tr>
<tr>
<td>Auto-immune disorders</td>
</tr>
<tr>
<td>Malignant lymphomas: Hodgkin, T-ALL, T-NHL</td>
</tr>
<tr>
<td>Mastocytosis</td>
</tr>
<tr>
<td>Solid tumors (GE-tumors, lung cancer)</td>
</tr>
<tr>
<td>Graft vs Host disease</td>
</tr>
</tbody>
</table>

Neoplastic/clonal HE and HES

WHO-defined myeloid malignancies with HE
- Chronic myeloid leukemia (CML-eo) |
- Myeloproliferative disorders (PMN-eo) |
- Systemic mastocytosis (SM-eo) |
- Myelodysplastic syndromes with HE (MDS-eo) |
- CBFb-fusion gene–related AML (AML-eo) |

Myeloid and hematopoietic stem cell malignancies
- PDGFRα rearrangement |
- PDGFRβ rearrangement |
- FGFR1 rearrangement |
- Other defects: PCM1-JAK2 fusion gene, FIP1L1 fusion gene |
- Eosinophilic leukemia e.c.t. |

 Syndromes associated with HE and HES

Gleich syndrome |
Churg-Strauss syndrome |
Ommen syndrome |
Eosinophilic-myalgia syndrome |
Hyper IgE syndrome |
Hereditary HE (not otherwise specified) |
HE of unknown significance (HEUS) |
Idiopathic HE |


If no obvious ‘reactive’ mechanism is identified, further exploration for a possible hematological malignancy is indicated. Malignancies associated with hypereosinophilia include chronic eosinophilic leukaemia, myeloproliferative disorders (chronic myeloid leukaemia or polycythaemia vera), variants of acute myeloid leukaemia (AML) and some lymphoproliferative disorders (Hodgkin lymphoma and T-cell lymphomas) and systemic mastocytosis. In the case of myeloid disorders, eosinophilia is clonal and part of the myeloid malignancy. On the other hand, when there is an underlying lymphoproliferative disorder, eosinophilia is polyclonal and frequently due to overproduction of IL-5. Sometimes, the underlying pathology of HE remains unclear even after extensive examination. In this case, the term ‘hypereosinophilia of unknown significance’ (HEUS) is used. The main characteristic of HEUS is the absence of eosinophil-related organ damage.

### Table 4. Most common parasitic infections associated with HE

<table>
<thead>
<tr>
<th>Parasites</th>
<th>Eosinophilia</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nematodes (roundworms)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascaris lumbricoides</td>
<td>Moderate/high at migration, low afterwards</td>
<td>Eggs in stool</td>
</tr>
<tr>
<td>Hookworms</td>
<td>High at migration, low/moderate afterwards</td>
<td>Eggs in stool</td>
</tr>
<tr>
<td>Strongyloides stercoralis***</td>
<td>Persistently high</td>
<td>Larvae in stool***, serology</td>
</tr>
<tr>
<td>Filaria species ****</td>
<td>Variable</td>
<td>Microfilariae***, serology</td>
</tr>
<tr>
<td>Trichinella species</td>
<td>Moderate/high</td>
<td>Serology, muscle biopsy</td>
</tr>
<tr>
<td>Angiostrongylus species</td>
<td>Moderate/high</td>
<td>Larvae CSF, PCR of CSF</td>
</tr>
<tr>
<td>Anisakis species</td>
<td>Moderate/high</td>
<td>Serology</td>
</tr>
<tr>
<td>Capillaria species</td>
<td>Variable</td>
<td>Serology, liver biopsy</td>
</tr>
<tr>
<td>Toxocara species</td>
<td>Moderate/high</td>
<td>Serology</td>
</tr>
<tr>
<td><strong>Cestodes (tapeworms)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taenia solium (cysticercosis)</td>
<td>Moderate/high at infection, low afterwards</td>
<td>Eggs/proglottids in stool, serology, ultrasound, CT</td>
</tr>
<tr>
<td>Echinococcus species</td>
<td>Moderate/high at infection, often absent afterwards</td>
<td>Serology, ultrasound, CT</td>
</tr>
<tr>
<td><strong>Trematodes</strong></td>
<td></td>
<td></td>
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<tr>
<td>Schistosoma species</td>
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<td></td>
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<tr>
<td>Fasciola hepatica</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonorchis sinensis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opisthorchis species</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paragonimus westermani</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High at invasion, moderate/low afterwards</td>
<td>Eggs in stool, serology</td>
<td></td>
</tr>
<tr>
<td>High at invasion, moderate/low afterwards</td>
<td>Eggs in stool, serology</td>
<td></td>
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<tr>
<td>High at invasion, moderate/low afterwards</td>
<td>Eggs in stool, serology</td>
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<td>Eggs in stool, serology</td>
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<tr>
<td>High at invasion, moderate/low afterwards</td>
<td>Eggs in stool, serology</td>
<td></td>
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<tr>
<td>Eggs in stool</td>
<td></td>
<td></td>
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<tr>
<td>eggs in stool or bile</td>
<td></td>
<td></td>
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<tr>
<td>eggs in stool</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protozoa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystoisospora belli</td>
<td>Questionable</td>
<td>Cysts in stool</td>
</tr>
<tr>
<td>Sarcozystis species</td>
<td>Variable</td>
<td>Cysts in stool, biopsy</td>
</tr>
<tr>
<td><strong>Ectoparasites</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scabies****</td>
<td>Questionable</td>
<td>Microscopic identification</td>
</tr>
</tbody>
</table>

* In the case of Strongyloides hyperinfection, hypereosinophilia can be absent.
** Strongyloides stercoralis larvae can be detected by the Baermann method (based on migration of larvae) or PCR.
*** Microfilariae can be detected in blood or skin, depending on the species.
**** Filaria species include among others, Brugia species, Wuchereria bancrofti, Loa loa, Mansonella ozzardi, Mansonella perstans and Mansonella streptocerca.
***** Eosinophilia is uncommon in classic scabies, and in approximately 50% of patients with crusted scabies, a marked eosinophilia may develop.
Note: Adapted from ‘Evaluation and differential diagnosis of marked, persistent eosinophilia’ by Nutman TB and ‘Eosinophilia in Infectious Diseases’ by O’Connell EM and Nutman TB.
Clinical manifestations

Depending on the underlying mechanism of HE or HES, a variety of clinical symptoms can occur. Essentially all organ systems can be affected, primarily skin, lungs, the digestive tract and heart.6 Most common presenting symptoms are fatigue (46%), coughing (24%), dyspnea (16%), myalgias and angioedema (14%), rash or fever (12%) and rhinitis (10%).3 Neurological deficits are also described, including muscle weakness and polyneuropathy. Special care should focus on the development of endomyocardial fibrosis (which is associated with risk of progressive heart failure) and thrombosis.

Diagnosis

Figure 1 presents an algorithm for the diagnostic work-up of HE which can be used in any clinical setting. Atopic constitution is often obvious from history and physical signs. An elevated serum level IgE or more specific tests such as radioallergosorbent or epicutaneous testing, further support this diagnosis. Pulmonary eosinophilia, which will not be discussed here, is a rare entity with both non-infectious (like allergic bronchopulmonary aspergillosis, acute and chronic eosinophilic pneumonias, Churg-Strauss syndrome) and infectious etiologies (mostly parasitic).1 A detailed history of used medication is important and should include the use of over-the-counter drugs, vitamins and supplements. For instance, in America, an epidemic of Eosinophilia–myalgia syndrome was linked to the use of L-tryptophan consumption.10 A travel history with sufficient exposure warrants a search for parasites. Serological methods are more sensitive and practical than the demonstration of eggs/cysts in stool. Particularly, HE is the immunological response to circulating worm antigens, which is most profound during the initial phase of infestation when larvae migrate through the organs and tissues of the host.7-9 Production of eggs detectable in varying quantities in stool samples is often apparent weeks later. When suspicion remains high, repeated testing is indicated. Bone marrow examination is indicated in all patients with unexplained and persistent HE and should include cytological assessment of the aspirate, immunohistochemistry, cytogenetics, FISH and molecular analysis. Screening of rearrangements of PDGFRα, PDGFRβ and FGFR1 is essential.3 The identification of the FIP1L1-PDGFRA fusion gene has to be performed with FISH or reverse transcription polymerase chain reaction (RT-PCR).
Furthermore, it is clinically relevant for all patients with persistent HE to screen for progression to HES and secondary organ failure. This often demands a multidisciplinary approach with different specialists in a consultative role. A thorough work-up by a cardiologist (echocardiography), dermatologist (skin biopsy) and neurologist may be advised.

**Treatment and follow up**

The first step in the management of HE is to identify and stop exposure to potential triggers such as medication and allergens. Parasitic infections require specific treatment, depending on type and stage of infection. Adequate treatment of *Strongyloides* infection with ivermectin is important because of the risk of *Strongyloides* hyperinfection. Repeated courses may be necessary to achieve full eradication. Empiric treatment with ivermectin 0.22 mg/kg in case of urgent need to initiate corticosteroid therapy, while results of serology are still pending, is justifiable. For patients with mild HE without signs of secondary organ damage, a wait-and-see policy can be justified. Regular follow-up is essential to evaluate progression to HES with subsequent organ damage. If treatment is indicated, systemic corticosteroids (0.5-1 mg/kg) are highly effective in rapidly reducing the eosinophil count. Concomitant use of corticosteroid-sparing agents, such as hydroxyurea and interferon-α, is often necessary because of side-effects and/or intolerance. Mepolizumab, an anti-IL-5 antibody, appeared to be safe and effective but is not currently approved by the Food and Drug Administration for HE(S). However, exceptional use for individuals with life-threatening HES who failed prior therapies, is described.

Patients with underlying hematological malignancies will generally fail to respond to steroids. Detailed discussion of different therapies is out of scope here. Referral to, or consultation of, a center of expertise is then recommended. When a *PDGFRα* or *PDGFRβ* fusion gene is established, treatment with imatinib can be started (tyrosine kinase inhibitor). A low dose of 100 mg per day is often sufficient to achieve molecular remission. Prompt treatment is necessary to prevent irreversible complications such as endomyocardial fibrosis and thrombosis. Patients with a FGRF1 mutation are often resistant to treatment with imatinib (response varies between 14-60%). Intensive chemotherapy followed by allogeneic stem cell transplantation is often recommended.

**CONCLUSION**

Hypereosinophilia is a rather frequently identified as laboratory abnormality. In most cases, there is an obvious identifiable cause, but sometimes more extensive exploration is necessary. A detailed history is still the most important first step in diagnosis. We must be aware of hematological malignancies and not hesitate to perform a bone marrow examination when the diagnosis remains unclear. Finally, in the case of persisting HE, we must always be aware of the progression to HES.

**REFERENCES**

Efficacy and safety of a phosphate replacement strategy for severe hypophosphatemia in the ICU

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Departments of 1Internal Medicine, 1Intensive Care, Rijnstate Hospital, Arnhem, the Netherlands; 2Intensive Care, University Medical Center Utrecht, the Netherlands
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ABSTRACT

Background: Experience with individualized phosphate replacement is limited in patients with severe hypophosphatemia. This study compares the efficacy and safety of an individualized regimen of serum phosphate < 0.4 mmol/l treatment in ICU patients to patients with moderate hypophosphatemia (0.4-0.6 mmol/l).

Methods: This retrospective cohort study included 36 patients with severe and 35 patients with moderate hypophosphatemia. Supplementation dose was calculated according to the equation: phosphate dose (in mmol) = 0.5 x body weight x (1.25 – [serum phosphate]). Sodium-potassium-phosphate was infused at a rate of 10 mmol/hour. Blood samples were taken at baseline and the next morning at 06.00 hrs.

Results: Serum phosphate rose to a level > 0.40 mmol/l in all patients with severe hypophosphatemia. Serum phosphate increased to > 0.60 mmol/l in 56% of patients with severe hypophosphatemia and in 86% of patients with moderate hypophosphatemia (p = 0.01). Mild hyperphosphatemia was observed in one patient only (1.53 mmol/l), hyperkalemia was observed in three patients (all three had severe hypophosphatemia, average potassium after supplementation was 5.2 ± 0.2 mmol/l) and serum calcium levels remained unchanged in both groups.

Conclusion: Individualized phosphate replacement was effective and safe for both moderate and severe hypophosphatemia, but was more accurate in moderate hypophosphatemia.

KEY WORDS

Hypophosphatemia, ICU, correctional algorithm, efficacy, safety

INTRODUCTION

Hypophosphatemia, an electrolyte disorder, is very common in ICU patients.1 Severe hypophosphatemia has been associated with respiratory and cardiac failure, difficult weaning from mechanical ventilation, rhabdomyolysis, neuropathy and thrombocytopenia.2-4 ICU and in-hospital mortality are increased in hypophosphatemic patients, in particular in those who develop phosphate levels < 0.40 mmol/l.5 Although a causal relationship between hypophosphatemia and mortality has not been firmly established, it is common practice to correct phosphate levels < 0.60 mmol/l by intravenous infusion of sodium-phosphate or sodium-potassium-phosphate (Na-K-P). Several replacement regimens have been proposed, mostly with fixed doses of phosphate.6 An exception is the recently proposed individualized replacement strategy using body weight, distribution volume and serum phosphate levels to calculate the required replacement dose.7 Evaluation of this strategy in our hospital in 50 ICU patients revealed high efficacy and safety.8 However, the majority of patients in this validation study had mild hypophosphatemia, whereas only 10 patients had a serum phosphate < 0.4 mmol/l. We therefore decided to extend the evaluation of this protocol in a larger group of patients with phosphate levels < 0.40 mmol/l, and to compare the results with patients who had phosphate levels between 0.40 and 0.60 mmol/l.

MATERIALS AND METHODS

This retrospective study was performed according to the regulations of the local ethics committee and performed in accordance with the Declaration of Helsinki, in a 15-bed ICU of a large teaching hospital in the Netherlands. The ICU population consisted of general medical and...
surgical patients. Exclusion criteria were: age < 18 years, serum creatinine > 150 mmol/l, serum total calcium corrected for albumin > 2.65 mmol/l, serum potassium > 4.5 mmol/l, phosphate not being replaced according to protocol and missing values after supplementation. The primary endpoint was the percentage of patients reaching a serum phosphate of > 0.6 mmol/l on the next morning at 06.00 hours after supplementation according to the algorithm.

Seventy-one ICU patients with a serum phosphate of < 0.60 mmol/l were included: 36 consecutive patients with severe hypophosphatemia (< 0.40 mmol/l) and 35 consecutive patients with moderate hypophosphatemia (0.40 - 0.60 mmol/l). Phosphate replacement was performed with sodium-potassium-phosphate (Na\textsubscript{2}K\textsubscript{5}PO\textsubscript{4}6: 1.5 mmol phosphate/ml), administered intravenously by infusion pump through a separate channel of a central venous catheter, at a fixed infusion rate of 10 mmol/h. Calculation of the total phosphate replacement dose was based on the actual serum phosphate level in mmol/l, a target level of 1.25 mmol/l and a phosphate distribution volume of 0.5 L/kg body weight, according to the following algorithm:

Phosphate dose in mmol = 0.5 x body weight x (1.25 – [serum phosphate]) (1)

Serum ionized calcium, creatinine, sodium, magnesium, phosphate and potassium were measured by routine clinical chemistry assays. Normal ranges are: calcium 1.10-1.32 mmol/l, creatinine 45-90 mmol/l, sodium 134-145 mmol/l, magnesium 0.7-1.10 mmol/l, phosphate 0.80-1.45 mmol/l and potassium 3.5-4.7 mmol/l.

Statistics

Results are shown as mean values ± standard error of the mean (SEM). Changes within a group, in response to treatment, were tested for normal distribution and compared with a paired t-test or Wilcoxon signed-rank test accordingly. Changes between groups were tested for normal distribution and analyzed by unpaired t-test or the Mann–Whitney U test. A p-value < 0.05 was considered to reflect statistical significance.

RESULTS

Baseline characteristics of both groups are summarised in Table 1. The two groups did not differ significantly, although a lower phosphate level was associated with a trend towards higher ICU-related mortality. Both groups had no significantly different baseline values for creatinine, potassium, sodium, ionized calcium or magnesium values. On average, the first phosphate measurement took place after a median of five hours (range 0-57 hrs) after ICU admission and hypophosphatemia was documented after a median of 56 hrs (range 4-1104 hrs). The calculated phosphate dose raised serum phosphate to a level > 0.40 mmol/l in all patients (Figure 1). Serum phosphate rose to a level > 0.60 mmol/l in 56% of

| Table 1. Baseline characteristics of patients with severe and mild hypophosphatemia. Data is represented as mean values ± SEM, unless otherwise indicated. *Survival is represented as ICU-survival. |
|---|---|---|
| **Serum phosphate** | \(< 0.4 \text{ mmol/l}\)| \(0.4 - 0.6 \text{ mmol/l}\) | \(p\)-value |
| Number of patients | 36 | 34 |  |
| Age (years) | 62.4 ± 2.4 | 65.4 ± 1.7 | 0.33 |
| Gender (f/m) | 18 / 36 | 15 / 34 | 0.40 |
| Body weight (kg) | 72.4 ± 3.7 | 76 ± 3.4 | 0.21 |
| Diagnosis ICU admittance (number of patients, %) | | | |
| • Infection | 13 (36.1%) | 11 (31.4%) | 0.68 |
| • COPD | 7 (19.4%) | 4 (11.4%) | 0.36 |
| • Cardiac arrest | 6 (16.7%) | 4 (11.4%) | 0.53 |
| • Post-surgical | 5 (13.9%) | 7 (20.0%) | 0.36 |
| • Other | 5 (13.9%) | 9 (25.7%) | 0.29 |
| APACHE-score | 24.5 ± 1.5 | 22.7 ± 1.3 | 0.36 |
| Survival* (number of patients, %) | 22 (65%) | 3 (82%) | 0.08 |

* = female; m = male; kg = kilogram; COPD = chronic obstructive pulmonary disorder; APACHE = Acute Physiology and Chronic Health Evaluation.

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patients with severe hypophosphatemia and in 86% of patients with moderate hypophosphatemia (p = 0.001). The mean phosphate level after supplementation was 0.75 ± 0.05 mmol/l in the group with severe hypophosphatemia, and 0.82 ± 0.03 mmol/l in the group with moderate hypophosphatemia (p = 0.03). The mean rise in serum phosphate was 0.38 ± 0.04 mmol/l in severe hypophosphatemia, versus 0.30 ± 0.03 mmol/l in the moderate hypophosphatemia group (p = 0.42). The mean phosphate replacement dose was 31 ± 3.9 mmol in patients with severe hypophosphatemia and 26 ± 1.8 mmol in patients with moderate hypophosphatemia (p = 0.02). The average duration of infusion was 167 ± 6.5 minutes. In patients with severe hypophosphatemia sodium-potassium-phosphate (Na-K-P), infusion caused a rise in serum potassium from 3.7 ± 0.1 mmol/l to 4.0 ± 0.1 mmol/l (p = 0.04), with three patients developing mild hyperkalemia (average potassium after supplementation: 5.2 ± 0.2 mmol/l), and induced mild hyperphosphatemia (1.53 mmol/l in one patient (2.8%). Neither creatinine, calcium, magnesium nor sodium levels changed significantly after supplementation (p = 0.69, p = 0.49, p

<table>
<thead>
<tr>
<th>Serum phosphate &lt; 0.4 mmol/l</th>
<th>Serum phosphate 0.4-0.6 mmol/l</th>
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<tbody>
<tr>
<td>Before supplementation</td>
<td></td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>70.6 ± 4.8</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>3.7 ± 0.1</td>
</tr>
<tr>
<td>Phosphate (mmol/l)</td>
<td>0.32 ± 0.01</td>
</tr>
<tr>
<td>Magnesium (mmol/l)</td>
<td>0.79 ± 0.03</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>1.15 ± 0.03</td>
</tr>
</tbody>
</table>
The level required to avoid redistribution of phosphate and ongoing renal phosphate and potassium loss. As blood samples were not taken immediately after the completion of infusion, we have no knowledge of the peak of phosphate and potassium levels and thus cannot reliably exclude the possibility that the incidence of transient hyperphosphatemia and hyperkalemia may be somewhat higher than we observed in the present study, based on measurements taken on the first morning after phosphate correction. In a previous study, we observed a post-infusion mean decline in serum phosphate of 0.3 mmol/l for a comparable post-infusion interval, and if we extrapolate this to the present study (see figure 1), we consider the risk of clinically significant hyperphosphatemia or hyperkalemia immediately after infusion to be very low.8 Furthermore, we did not test our algorithm in patients with a serum creatinine > 150 mmol/l. However, since these patients usually retain phosphate rather than excrete it via the urine, the number of patients with a high serum creatinine and hypophosphatemia will probably be small.

CONCLUSION

The individualised replacement regimen was safe and effective for both mild and severe hypophosphatemic patients. After infusion, all patients with severe hypophosphatemia reached phosphate levels > 0.40 mmol/l. Although 44% of the patients with severe hypophosphatemia did not reach the target serum phosphate of > 0.60 mmol/l, higher phosphate replacement doses are not recommended because of the risk of inducing hyperphosphatemia. We advise to perform repeated daily doses in these patients.

ACKNOWLEDGEMENTS

All authors declare no conflict of interest. No funding or financial support was received.

REFERENCES

Macrophage activation syndrome with lung involvement complicating adult-onset Still’s disease

C.R. Wang*, Y.S. Tsai†, I.C. Ma‡

ABSTRACT

Adult-onset Still’s disease (AOSD) can progress into macrophage activation syndrome (MAS), which may be fatal. We report on a 19-year-old Han Chinese female, who presented with MAS-related pulmonary parenchymal involvement complicating AOSD, and further associated with disseminated intravascular coagulation and generalized tonic-clonic seizure. She was managed by high-dose corticosteroids and pulse cyclophosphamide therapy with a complete recovery of disease activity.

KEY WORDS

Adult-onset Still’s disease, AOSD, macrophage activation syndrome, pulmonary involvement

INTRODUCTION

Adult-onset Still’s disease (AOSD) was first reported in 1971 by Eric Bywaters in 14 adult patients who failed to fulfill the criteria of classic rheumatoid arthritis. It is a rare systemic auto-inflammatory disorder with high spiking fever, evanescent skin rash, arthralgia/arthritis, neutrophilic leukocytosis and marked hyperferritinemia. Despite a usually favorable prognosis in AOSD, patients can experience disease flares which involve vital organs, or present specific clinical features, such as macrophage activation syndrome (MAS). Here, we report on an AOSD patient with MAS-related pulmonary parenchymal involvement who was successfully managed by high-dose corticosteroids and pulse cyclophosphamide therapy.

CASE REPORT

A 19-year-old Han Chinese female was presented with polyarthritis affecting her wrists, knees and ankles, and a recurrent maculopapular erythematous rash over her trunk and limbs during febrile spikes (above 39°C). Laboratory tests revealed leukocytosis (10,600 to 15,800/µl) with dominant neutrophil classification (82 to 92%), elevated liver enzyme levels, absence of autoantibody profiles and negative microbiological examinations. One year later, she
visited the outpatient rheumatology clinic with a series of clinical, laboratory and radiological surveys, leading to the diagnosis of AOSD by exclusion of infection, malignancy or other rheumatologic diseases. She was brought to the emergency department one month later due to a cough and dyspnea, where radiological images demonstrated diffuse peribronchovascular infiltrates, multiple ground-glass opacities and consolidations in her lower lungs without pleural effusion (figures 1A and B), as well as hepatosplenomegaly. Hemogram was hemoglobin = 8.0 g/dl, platelet count = 25,000/µl and leukocyte count = 9,300/µl (neutrophils 63%), and bone marrow examination revealed hemophagocytosis. She exhibited elevated levels of aspartate aminotransferase (1,115 U/l), alanine aminotransferase (311 U/l), ferritin (9,655 ng/mL), triglycerides (388 mg/dl) and impaired estimated glomerular filtration rate (22 ml/min/1.73 m²) with unremarkable urinalysis. Pathogenic microorganisms were not isolated despite extensive cultures. MAS complication was identified with the prescription of methylprednisolone 20 mg, every eight hours by injection. However, bloody sputum with a significant drop of hemoglobin led to a suspicion of diffuse alveolar hemorrhage. Multiple petechiae and hematuria with global coagulation tests fulfilled the disseminated intravascular coagulation criteria, followed by attacks of generalized tonic-clonic seizure; both are distinct AOSD-related MAS presentations. A monthly pulse cyclophosphamide 750 mg infusion was initiated due to progressive pulmonary infiltration (figure 1C) and persistent multi-organ abnormalities. The patient had a complete recovery of lung involvement (figure 1D) and other systemic dysfunction with daily corticosteroids replaced by weekly methotrexate therapy during outpatient follow-up.

**DISCUSSION**

Unlike other rheumatology disorders involving multiple organs with known respiratory abnormalities, little attention has been paid to lung involvement in
AOSD. By excluding the infectious etiology, pulmonary infiltrates have been observed in fewer than one-tenth of AOSD patients, with its acute nature accompanied by pleural effusion during disease exacerbation and a fast response to corticosteroids usage. In a recent literature review including 18 AOSD cases with parenchymal lung involvement, two with MAS were successfully managed by corticosteroids alone. In another review with nine cases of corticosteroid-resistant AOSD-associated MAS significant responses were observed in all 5 patients receiving cyclophosphamide injection, despite no associated pulmonary parenchymal involvement. In the reported patient with progressive pulmonary infiltration under the high-dose corticosteroid therapy, adding cyclophosphamide resulted in complete recovery. Notably, biologics have proven to be safe and effective in the long-term management of AOSD, particularly in cases with systemic involvement. Since MAS is characterized by a cytokine storm with overproduction of pro-inflammatory cytokines, anti-cytokine agents are an attractive approach in treating this complication. Indeed, in young female victims, cytokine blockades as alternative therapeutics can avoid the well-known cyclophosphamide-related gonadal toxicity.

DISCLOSURES
All authors declare no conflict of interest. There was no funding or financial support in this report.

REFERENCES
Central diabetes insipidus: beware of Langerhans cell histiocytosis!

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disorder, characterised by a monoclonal proliferation of aberrant histiocytes that accumulate in and infiltrate into different organs. When the hypothalamic-pituitary axis is involved, central diabetes insipidus (CDI) can be its first manifestation. Three cases of LCH with central diabetes insipidus were retrospectively analyzed:

Case 1 is a 41-year old female presenting with polyuria and polydipsia. Diabetes insipidus was diagnosed and treated with desmopressin. MRI pituitary showed hypophysitis. Subsequently, she developed bone lesions and a biopsy demonstrated LCH.

Case 2 is a 51-year old female presenting in 2009 with polyuria and polydipsia. Diabetes insipidus was diagnosed and treated with desmopressin. MRI pituitary revealed hypophysitis. LCH was suspected because of known pulmonary histiocytosis. Coexisting bone lesions were biopsied and confirmed LCH.

Case 3 is a 44-year old female presenting with diabetes insipidus. She was treated with desmopressin as well. MRI of the pituitary gland showed impressive thickening of the infundibulum. A few months later, she developed skin lesions and a biopsy revealed LCH.

Conclusively, LCH is a rare, elusive and probably underdiagnosed disease with a broad disease spectrum. Due to infiltration of the hypothalamic-pituitary axis, CDI can be the first manifestation, even before LCH is diagnosed. Therefore, LCH should be considered in the diagnostic workup of CDI.

KEY WORDS

Diabetes insipidus, hypothalamic-pituitary axis, Langerhans cell histiocytosis

What was known on this topic?

Langerhans cell histiocytosis is a rare and still partly elusive disease with a very broad disease spectrum ranging from isolated and indolent symptoms to multisystem and life-threatening conditions. Nevertheless, systemic treatment can be curative.

What does this add?

This article adds that central diabetes insipidus can be the first manifestation of Langerhans cell histiocytosis (LCH), even long before LCH is diagnosed. Therefore, LCH should be considered in the CDI diagnostic workup.

INTRODUCTION

Diabetes insipidus (DI) is a disorder of water balance in the kidneys, characterized by a failure to concentrate urine, causing polyuria (i.e. > 2 l/m²/24h) and subsequently polydipsia. DI is subdivided into central and nephrogenic DI. Central diabetes insipidus (CDI) arises from destruction or degeneration of magnocellular neurons in the paraventricular and supraoptic nuclei, which are responsible for producing vasopressin. If more than 80% of these cell bodies are damaged, polyuria occurs because of vasopressin deficiency. In contrast, nephrogenic DI is the result of an impaired kidney response to vasopressin. The broad differential diagnosis of CDI makes it challenging to determine its underlying aetiology (table 1). One cause of CDI is Langerhans cell histiocytosis (LCH), which can appear with variable presentation. We demonstrate this by describing three different patients with LCH.
S U B J E C T S  A N D  M E T H O D S

Three cases of LCH with CDI were retrospectively analysed in the outpatient clinic of the University Hospital in Brussels from 1996 until 2017. Patient characteristics, clinical presentation, diagnosis and treatment were compared (table 2).

R E S U L T S

Case histories

Case 1: In 2009, a 41-year-old woman presented with polyuria and polydipsia. A water deprivation test confirmed the diagnosis of CDI, and magnetic resonance imaging (MRI) of the pituitary gland showed hypophysitis. Desmopressin treatment was started. In 2014, she developed skeletal pain and a fever. Positron emission tomography with 2-deoxy-2-fluorine-18-fluoro-D-glucose and computed tomography (18-FDG PET/CT) showed various bone lesions. Histological examination of lesional tissue at the right acromion showed positive CD1a and protein S100 staining; polymerase chain reaction (PCR) demonstrated a proto-oncogene BRAFV600E mutation matching the diagnosis of LCH. In the meantime, the patient also developed hypogonadotropic hypogonadism. Systemic treatment with vinblastine and prednisone was initiated, although suspended after six weeks because of toxicity. In 2015, new bone lesions were resected and although systemic treatment was repeatedly proposed because of multisystemic disease, the patient declined this.

Case 2: A 51-year-old woman with known pulmonary histiocytosis since 2004 developed polyuria and polydipsia in 2008. CDI was confirmed through a positive water deprivation test, and MRI of the pituitary gland demonstrated hypophysitis. Desmopressin treatment relieved her symptoms. A diagnostic technetium bone scintigraphy revealed lesions at the mandibula and skull. LCH was confirmed upon histological examination of the mandibular lesion expressing CD1a and protein S100 antigens. At the time, mutational analysis was not routinely performed to diagnose LCH. Therefore, we do not have any mutational data of the lesional tissue. The bone lesions were resected and although systemic treatment was proposed because of multisystemic disease, the patient declined this.

Case 3: A 44-year-old woman presented in 1996 with polyuria and polydipsia. A water deprivation test confirmed the diagnosis of CDI, and MRI of the pituitary gland showed an impressive thickening of the infundibulum. Simultaneously, coexisting hypogonadotropic hypogonadism and central hypothyroidism were diagnosed. Desmopressin treatment and substitution therapy with levothyroxine and an oral contraceptive pill achieved good results. A few months later, she developed skin lesions. Underlying LCH was identified through electron microscopy and histological examination of a skin biopsy, showing typical Birbeck granules and protein S100 positivity, respectively. No mutational data are available for this case either. Corticosteroids and azathioprine treatment caused the lesions to disappear. Nevertheless, it was necessary to continue treatment for CDI and anterior pituitary function loss.

D I S C U S S I O N

The above-described three patients demonstrate the highly variable presentation of LCH, in which the common denominator is the development of CDI. LCH is a rare disease and can occur at any age, although it is more frequently seen in children with a male predominance. Its incidence is approximately five cases per million children and about one or two cases per million adults. General clinical presentation of LCH can be highly variable depending on which organ is infiltrated, and the disease spectrum ranges from isolated skin or skeletal lesions to multisystem involvement and sometimes life-threatening conditions such as acute lymphoblastic leukaemia. A four-part LCH classification has been established by the Histiocyte Society (table 3).

The origin, development and regulation of LCH is complex and unravelling the molecular mechanisms that govern these processes are important for accurate diagnosis and treatment. LCH is characterized by a specific histopathological lesion containing clonal Langerhans-type cells, which can be recognized by their expression of CD1a, S100 protein, langerin (CD207) and Birbeck...
<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Medical History</th>
<th>Presentation CDI</th>
<th>MRI Imaging</th>
<th>Initial Treatment</th>
<th>Biopsy: LCH</th>
<th>Other Manifestations</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>41</td>
<td>F</td>
<td>Obesity, laparoscopic gastric banding, hip prosthesis left, eczema</td>
<td>2009: Polyuria and polydipsia</td>
<td>Hypophysitis</td>
<td>Desmopressin intranasally</td>
<td>2014: Acromion right IHC: CD1a+, S100+ PCR: BRAFV600E+</td>
<td>MRI: Diffuse enlargement of pituitary (i.e. &gt; 3 mm)</td>
<td>2014: Hypogonadotrophic hypogonadism; diffuse bone lesions: right shoulder, left clavicle, left hip, L2 2015: Bone lesions at both knees, left shoulder, sacroiliac joint</td>
<td>2014: Vinblastine/ prednisone§ 2015: Dabrafenib 150 mg 2x/d and trametinib 2mg 1x/d‡</td>
</tr>
<tr>
<td>#2</td>
<td>51</td>
<td>F</td>
<td>Hysterectomy, pneumothorax right treated with talcage, pulmonary LCH, nicotine dependence</td>
<td>2008: Polyuria and polydipsia</td>
<td>Hypophysitis</td>
<td>Desmopressin intranasally</td>
<td>2004: Lung (no data) 2010: Mandibule IHC: CD1a+, S100+ PCR: No mutation data¶</td>
<td>MRI: Diffuse enlargement of pituitary (i.e. &gt; 3 mm)</td>
<td>2004: Pulmonary cysts 2010: Mandibular cyst + 1 skull lesion 2014: 2 skull lesions 2017: Relapse pneumothorax</td>
<td>2004: Smoking cessation† 2010: Surgical cyst resection</td>
</tr>
<tr>
<td>#3</td>
<td>44</td>
<td>F</td>
<td>None</td>
<td>1996: Polyuria and polydipsia</td>
<td>MRI: Impressive thickening of infundibulum (&gt; 3mm)</td>
<td>Desmopressin intranasally</td>
<td>1996: Skin IHC: S100+, no CD1a data§ EM: Birbeck granules PCR: no mutation data¶</td>
<td>H&amp;E: Skin infiltrate</td>
<td>1996: Corticoids, azathioprine 50 mg, Levothyroxine and gestodene/ ethinyl-estradiol</td>
<td>CR of skin lesions, persisting CDI, hypothyroidism and secondary amenorrhea</td>
</tr>
</tbody>
</table>

IHC: immunohistochemistry; PCR: polymerase chain reaction; EM: electron microscopy; H&E: hematoxylin and eosin stain; CR: complete remission
§ At the time, vinblastine/prednisone was administered, based on established protocols for multisystem LCH in children. It was suspended because of neurotoxicity. Vinblastine is currently known to be less effective and has higher toxicity rates in adults.
‡ Dabrafenib (BRAF inhibitor), trametinib (MEK inhibitor). Combination therapy with trametinib instead of dabrafenib monotherapy was chosen to eliminate the incidence of known BRAF inhibitor-induced palmoplantar hyperkeratosis and secondary skin malignancies at higher dosages.
¶ These cases date from before determination of recurrent mutations in LCH. Since these biopsies are no longer accessible; post hoc mutation analysis was not possible.
† After smoking cessation, pulmonary lesions remained stable and did not affect pulmonary function tests. No systemic treatment was administered at the time.
§ CD1a data and biopsy no longer available.
Langerhans cell histiocytosis classification according to the Histiocyte society

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Description</th>
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<tbody>
<tr>
<td>LCH – SS</td>
<td>A single organ is affected; no lung or risk organ involved.</td>
</tr>
<tr>
<td>LCH lung</td>
<td>Lung involvement but no risk organ.</td>
</tr>
<tr>
<td>LCH – MS – RO</td>
<td>Multiple systems affected but no lung or risk organ involved.</td>
</tr>
<tr>
<td>LCH – MS – RO</td>
<td>Multiple systems affected and at least one risk organ involved.</td>
</tr>
</tbody>
</table>

Four different subtypes of LCH are defined by the Histiocyte Society depending on the number and kind of organs (systems) involved. Risk organs (RO) are the spleen, liver or the hematologic system.

LCH = Langerhans cell histiocytosis; SS = single system; MS = multiple systems; RO = risk organs.

granules. Interestingly, based on their gene expression profile these pathological histiocytes do not correspond to epidermal Langerhans cells, but rather originate from myeloid-derived precursor dendritic cells. A 2010 report demonstrated recurrent genetic abnormalities in clonal LCH cells, establishing LCH as a neoplasm.

To date, the two most prevalent mutations are found in either the proto-oncogenes BRAF (BRAF^{V600E}) or MAP2K1. These mutations result in a constitutive activation of the mitogen-activated protein kinase (MAPK) pathway causing pathological proliferation and differentiation. However, not all responsible genes have yet been discovered.

The endocrine system can also be affected by LCH, as Langerhans cells can migrate to the lymph nodes and affect the hypothalamic-pituitary axis. This can lead to mostly irreversible CDI with corresponding symptoms of polyuria and polydipsia. In Patient 1 and 3, CDI was the first presenting feature of LCH and in patient 2, CDI developed later in the course of the disease.

A positive water deprivation test can confirm the diagnosis of CDI. An MRI, typically shows a lack of the hyper-accentuated signal of the posterior pituitary on sagittal T1-weighted imaging and a thickening of the pituitary stalk. Infiltrative disease of the pituitary gland can lead to thyrotropic, somatotropic or gonadotropic axis failure. The prevalence of CDI in patients with LCH ranges from 10-50% and CDI presents in most cases after the diagnosis of LCH is established. In addition, CDI occurs more frequently in patients with BRAF^{V600E}.

Treatment options for LCH differ because of its wide disease spectrum. They range from minimal conservative treatment in single skin or bone disease to intensive combination chemotherapy in multisystem disease. However, vinblastine/prednisone treatment for one year is the standard initial systemic regimen for children. Adults, conversely, are preferably treated with cytarabine (second-line) because of poor overall responses and excessive toxicity of first-line chemotherapy. Targeted therapy with inhibitors of the BRAF/MAPK pathway (i.e. vemurafenib or trametinib, respectively) can be used in patients with corresponding mutations in whom first-line therapy fails; BRAF^{V600E} is associated with more resistant LCH and higher reactivation rates in response to first-line treatment. LCH-induced CDI is treated with desmopressin. LCH prognosis depends on the extent of the disease, and disseminated disease may still have serious and even fatal outcomes.

CONCLUSIONS

Our three patients clearly demonstrate that the diagnosis of LCH can be challenging and is sometimes made after a long clinical history. Occasionally, CDI arises as primary manifestation before LCH is known. Furthermore, although most publications report a male and pediatric predominance, our three cases presented females in their 40s and 50s. LCH is a rare disorder with a broad disease spectrum, and a more comprehensive understanding of the LCH etiopathogenesis may lead to alternative therapeutic interventions in the future.
ACKNOWLEDGMENTS

All authors declare no conflict of interest. No funding or financial support was received.

REFERENCES

PHOTO QUIZ

Crusted cutaneous lesions requiring early diagnosis and appropriate treatment

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CASE REPORT

A 71-year-old woman with a medical history of breast cancer but lost to follow-up was admitted to the hospital for fatigue, loss of autonomy and pulmonary infection treated with cefotaxime. On clinical examination, she was cachectic with a temperature of 38°C. Asymptomatic crusted lesions with fissuring were present over her extremities, in particular, on her feet, including the nails and legs (figure 1), and on her hands at the interdigital webspaces (figure 2); however, she presented with no scalp or mucosal lesions. Blood cell count, serum creatinine level and urinalysis, liver function tests, thyroid-stimulating hormone were within normal range; serum electrophoresis showed an albumin level of 15/l (normal > 35), C reactive protein was 67 mg/l (normal < 5) and HIV testing was negative.

WHAT IS YOUR DIAGNOSIS?

See page 451 for the answer to this photo quiz.

Figure 1. Crusted lesions over the legs and feet with nail involvement

Figure 2. Hyperkeratotic lesions over the dorsum aspect of the hands especially on the interdigital web spaces
DIAGNOSIS

A diagnosis of crusted scabies (also called Norwegian scabies) was determined based on the patient’s cutaneous lesions, although diagnoses of paraneoplastic syndrome, hypothyroidism and psoriasis were also discussed. Indeed, dermatoscopic and microscopic examinations of skin scrapings from the feet and hands revealed mites consistent with *Sarcoptes scabiei*. The crusted scabies were treated with oral ivermectin and 5% permethrin cream. No source of infection was found, and no other case was diagnosed, except for her daughter, who received appropriate treatment. The caregivers and patients in contact with the patient were preventively treated with ivermectin and no one developed the infection while under the care of the hospital’s Nosocomial Infection Control Committee. The patient suddenly died a few days later of unknown cause.

Scabies is a common parasitic infestation due to *Sarcoptes scabiei* variety hominis, an obligate ectoparasite. Clinical lesions are produced by female mites that deposit their eggs and fecal pellets in the epidermis, which leads to a delayed-type hypersensitivity reaction. In healthy patients, this condition is transmitted by direct, prolonged skin-to-skin contact or indirect contact through infested bedding and clothing, and also via staff in nursing homes and hospitals with frequent and repeated contact. It usually presents with itching lesions over the anterior aspect of the wrists, interdigital webspaces, nipples, axillae and penis, and can be caused by only a few mites. Conversely, crusted scabies is a hyperinfestation affecting immunocompromised and mentally or physically disabled patients; it rarely affects healthy individuals. Patients present with lack of itching or poorly itching crusted lesions involving the palms and soles, flexor surfaces of the legs and nails and scalp, with hundreds or millions of lesions. It is highly infectious and can be transmitted after a brief skin-to-skin contact, and also from contact with bedding, clothing, furniture and floors contaminated with skin scales and crusts containing mites from the patient. Indeed, outbreaks can occur in healthcare and residential facilities. Diagnosis of scabies can be established upon clinical examination but definite diagnosis relies on microscopic examination of skin scrapings disclosing mites and eggs. Of note, dermatoscopy can visualize both the burrow and the mite itself, with hang glider-like triangles corresponding to the mite’s head and round body corresponding to the mite’s abdomen. Differential diagnosis includes psoriasis, eczema, hypothyroidism and ichthyosis.

Treatment of common scabies relies on 5% permethrin cream or oral ivermectin and disinfection of the environment including clothes and bed linens in contact with the patient during the previous 72 hours, washed at 60°C or placed into a sealed plastic bag with insecticide. Treatment of close personal contacts including household members, sexual partners, other patients and staff is necessary. For patients with crusted scabies topical permethrin, keratolytics and oral ivermectin should be given for at least 15 days with re-evaluation and additional doses if necessary. It is essential that care providers wear protective garments including gowns, long-sleeve gloves and shoe covers during any contact with patients with crusted scabies. Visitors should also wear protective garments and be limited to one person per visit. Environmental disinfection is required, in particular, regular room cleaning of the patient to remove contaminating skin crusts and scales. A public health agency can help manage these situations outside the hospital. In our hospital, the parasitologists, members of the Nosocomial Infection Control Committee, provided information, screened and treated staff, patients and household members and checked contact precautions.

References

PHOTO QUIZ

Progressive visual decline in a Rotterdam harbor crane operator

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CASE REPORT

A 74-year-old male was admitted to the hospital complaining of progressive visual decline. Medical history revealed diabetes mellitus, atrial fibrillation, hypercholesterolemia and gout. He worked as a crane operator in the harbor of Rotterdam, the Netherlands. At presentation, he reported a weight loss of 10 kg in the last three months. Visual acuity was 0.16 in both eyes. Initial laboratory investigation revealed a significantly raised erythrocyte sedimentation rate (128 mm/h) but otherwise no abnormalities. Computed tomography and magnetic resonance imaging of the brain showed no significant abnormalities. The ophthalmologist performed fundoscopy and fluorescein angiography (figures 1A and 1B).

WHAT IS YOUR DIAGNOSIS?

See page 453 for the answer to this photo quiz.
DIAGNOSIS

Fundoscopy and fluorescence angiography demonstrated papilledema and posterior uveitis, which may include optic neuritis from neurosyphilis in its differential diagnosis, but may also be due to central retinal artery or vein occlusion or elevated intracranial pressure because of a tumor, hypertension, a subarachnoid hemorrhage or a subdural hematoma. The patient denied casual male sexual contact and had no history of sexually transmitted diseases. He could not remember having had a chancre or other clinical features of syphilis, and HIV testing was negative. Rapid pathogen reagin (RPR) testing and a treponema pallidum (TP) antibody test was positive in blood samples with an RPR titer of 1:64. Cerebrospinal fluid (CSF) tested negative for RPR but positive for TP Western blot. CSF also showed decreased glucose (2.1 mmol/l), increased protein (0.61 g/l), increased white blood cell count (12 x 10³/μl) and an increased immunoglobulin G (IgG) index (0.72). Hence, a diagnosis of neurosyphilis-associated posterior uveitis with papilledema was made and treatment was started with intravenous (i.v.) benzylpenicillin of three million international units, six times daily. However, visual abilities did not improve after two weeks of treatment. After deliberation, 60 mg prednisolone orally, once-daily has been found to be effective in the management of syphilis may avoid/diminish the Jarisch-Herxheimer reaction, a hypersensitivity reaction caused by penicillin-induced spirochete death. Anecdotal case reports suggest that topical, periocular and systemic CSs may have an adjunctive role in the management of ocular syphilis, perhaps by suppressing intraocular inflammation and reducing uveitic macular edema. Adjunctive topical CSs have been found to be effective in the management of interstitial keratitis and anterior uveitis. Additional oral and i.v. CSs are used to treat posterior uveitis, scleritis and optic neuritis and led to notable improvement of visual ability in the present case.1,4,6

PRIMARY TREATMENT OF SYphilis INvolves high-dose i.v. penicillin. In addition, the use of corticosteroids (CSs) in syphilis may avoid/diminish the Jarisch-Herxheimer reaction, a hypersensitivity reaction caused by penicillin-induced spirochete death. Anecdotal case reports suggest that topical, periocular and systemic CSs may have an adjunctive role in the management of ocular syphilis, perhaps by suppressing intraocular inflammation and reducing uveitic macular edema. Adjunctive topical CSs have been found to be effective in the management of interstitial keratitis and anterior uveitis. Additional oral and i.v. CSs are used to treat posterior uveitis, scleritis and optic neuritis and led to notable improvement of visual ability in the present case.1,4,6

REFERENCES

LETTER

Moderate increase of serum levels of procalcitonin in diabetic ketoacidosis

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To the editor,

Procalcitonin (PCT) is a helpful marker of systemic inflammatory response to an infection and when detected at levels higher than 2 ng/ml, it is strongly indicative for sepsis of bacterial aetiology. Mild PCT elevations are also detected in many other diseases such as viral infections, autoimmune disorders, myocardial infarction, stroke, burns and multiple trauma.

It is well-established that diabetic ketoacidosis (DKA) is associated with leukocytosis and an increase in acute phase proteins, including C-Reactive Protein (CRP), tumor necrosis factor alpha, interleukin 1 beta (IL-1β), IL-2, IL-6 and IL-8. Since infections are the most common precipitating factors in the development of DKA in patients affected by diabetes, it is of paramount importance to rule out bacterial infection.

In this letter, we report the case of a young woman with type 1 diabetes who presented at our emergency department with vomiting and intense abdominal pain. She had not taken her usual dose of insulin therapy the night before because of malaise. Based on her clinical presentation, as well as her arterial blood gas results (high anion gap metabolic acidosis) and her plasma glucose levels (~ 29 mmol/l), she was diagnosed with DKA. Interestingly, PCT concentration was moderately increased (1.72 ng/ml at presentation and 2.31 ng/ml the day after), no occult infection was detected (chest X-ray, abdominal ultrasound, and urine dipstick) and the patient remained afebrile. Classic treatment for DKA was applied (hydration, intravenous insulin and potassium administration) without administration of any antibiotic, and the patient demonstrated rapid clinical improvement. PCT returned to normal values (< 0.5 ng/ml) after three days of hospitalization, reflecting the half-life of the protein.

Previous studies have suggested that increased PCT and hyperglycemia may be interrelated. In a large cohort (n = 66i8), Abbasi and colleagues demonstrated that PCT is a predictor of incident type 2 diabetes independent of common risk factors such as gender, smoking, waist circumference, hypertension and familial diabetes. Moreover, it has also been reported that correction of plasma glucose levels leads to a decrease of PCT concentrations in patients presenting with acute hyperglycemia. To our knowledge, increased PCT levels within the context of DKA has only been reported once before: In a large retrospective study investigating the discrepancies in the increase of CRP and PCT concentrations in children and adolescents during acute illness, Ivaska et al. reported that there were mild-to-severe increases of PCT concentrations in four children with DKA. None of them had clinical signs of bacterial infection.

The role of acute phase proteins, including PCT, within the context of DKA warrants further investigation. Furthermore, practitioners should be aware that increases in CRP and PCT may occur in patients with DKA in the absence of a concomitant infection thus, avoiding unnecessary examinations such as blood cultures and treatments (antibiotics) if other signs of infection are absent.

REFERENCES

To the editor,

Many patients sent to the emergency department for various reasons, undergo a chest X-ray. Patients are sometimes too sick or otherwise unable to stand up straight. In these cases, a so-called “bed photo” is made, and even then, some patients are not able to sit up straight or hold their head straight. During morning rounds this phenomenon was called the “nodding head” and in a clinical setting this could indicate upcoming death. This observation was substantiated in a prospectively collected dataset; only patients above the age of 65 were included in this study. A “nodding head” was defined as superposition of the lower jaw over the anterior border of the superior thoracic aperture, defined as the place where the clavicles articulate with the sternum. In 2014, a total of 2653 chest X-rays were performed in the emergency department. Of these, 1399 (52%) X-rays were made of patients over the age of 65 years, and of these, 677 (48%) images were “bed-photos”. Hospital records were studied in order to gather data on morbidity and probable cause of death or co-morbidity that contributed to death. Data on mortality were collected by the end of the year 2015 in order to obtain sufficient follow-up. Overall mortality, as well as 30-day mortality, was studied. The “nodding head” group comprised of 90 patients; 65 patients died (72%), compared to 296 deaths (50%) of the 587 patients without

<table>
<thead>
<tr>
<th>Table 1. Causes of death or co-morbidity in patients with or without a “nodding head”</th>
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</thead>
<tbody>
<tr>
<td><strong>“Nodding head”</strong> n = number of patients (%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Pulmonary disease</td>
</tr>
<tr>
<td>Neurological disorder</td>
</tr>
<tr>
<td>Miscellaneous (cause of death not to be determined)</td>
</tr>
<tr>
<td>Mixed (more than one co-morbidity)</td>
</tr>
</tbody>
</table>

Figure 1. A shows the 30-day mortality, while in B the overall mortality is shown.
a “nodding head”. This difference is statistically significant ($p < 0.0001$) (figure 1). Table 1 shows co-morbidity and the disease that most likely lead to death. Patients with a “nodding head” died more often due to pulmonary diseases, while patients with normal head position died more often because of cancer. From this observational study, it can be concluded that a patient with a “nodding head” is in worse clinical condition and is prone for death within the next few months. A “nodding head” could be seen as an additional practical prognostic factor in elderly patients.