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BRIEF REPORT

Whipple's disease in granulomatous disguise: a challenging diagnosis with many histopathological pitfalls

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Introduction

Whipple's disease is a rare systemic illness caused by *Tropheryma whipplei*, a Gram-positive bacterium. Despite its abundant natural prevalence and reports on frequent asymptomatic carriage of *T. whipplei*, Whipple's disease has an estimated annual incidence between only one and six per 10 million populations. This disease predominantly affects middle-aged white males [5, 6, 9]. Specific HLA constellations predispose to the development of Whipple's disease by hampering the protective immune response that occurs in most infected individuals [5]. Impaired function of intestinal macrophages prevents the degradation of *T. whipplei* and results in massive accumulation of macrophages, laden with this intracellular pathogen, in the lamina propria of the small intestine [6]. Early reports on Whipple's disease describe a "classic" form, characterized by gastrointestinal symptoms such as diarrhea, malabsorption, abdominal pain, and weight loss [10]. Occasional case reports in the past decades have broadened our view on the clinical presentation, since they showed that Whipple's disease can mimic many other conditions. Therefore, diagnosis is often delayed [1, 3, 8, 12].

Here, we describe an atypical presentation of Whipple's disease, concerning a man who initially presented with cervical lymphadenopathy only. At first, he was misdiagnosed with sarcoidosis, a mimic of Whipple's disease. Several biopsies were performed during the diagnostic process. Here, we discuss potential diagnostic pitfalls based on the obtained histopathological images.

Case report

In January 2013, a 33-year-old man presented in an outside hospital with prominent bilateral cervical lymphadenopathy, without any other symptoms. Computed tomography (CT) of the thorax showed limited mediastinal lymphadenopathy. A cervical lymph node biopsy was performed, which showed replacement of the normal nodal architecture by numerous epithelioid non-caseating, sarcoid-like granulomas. Some granulomas contained Schaumann bodies (Fig. 1a). Polarized light microscopy confirmed the presence of calcium oxalate crystals (Fig. 1b), which are often observed in sarcoidosis. A Mantoux test was negative, and cultures of lymph node aspirates were negative for mycobacteria. Serology for *Bartonella* species was negative. A tentative diagnosis of sarcoidosis was established. The patient was not treated with corticosteroids since there were no respiratory symptoms and pulmonary function testing was normal. Moreover, a yet undetected infection was included in the differential diagnosis, and treatment with corticosteroids was relinquished because it could have worsened its clinical outcome. Follow-up was advised. Seven months later, pulmonary function tests were repeated and did not show any anomalies. The patient mentioned a slight loss of appetite and a weight loss of 4 kg.

In the following 3 years, the patient experienced relapsing submandibular and cervical lymphadenopathy. Additionally, he progressively developed migratory arthralgia and myalgia, drenching night sweats, severe fatigue, and an inexplicable weight loss of 15 kg since the initial clinical contact.

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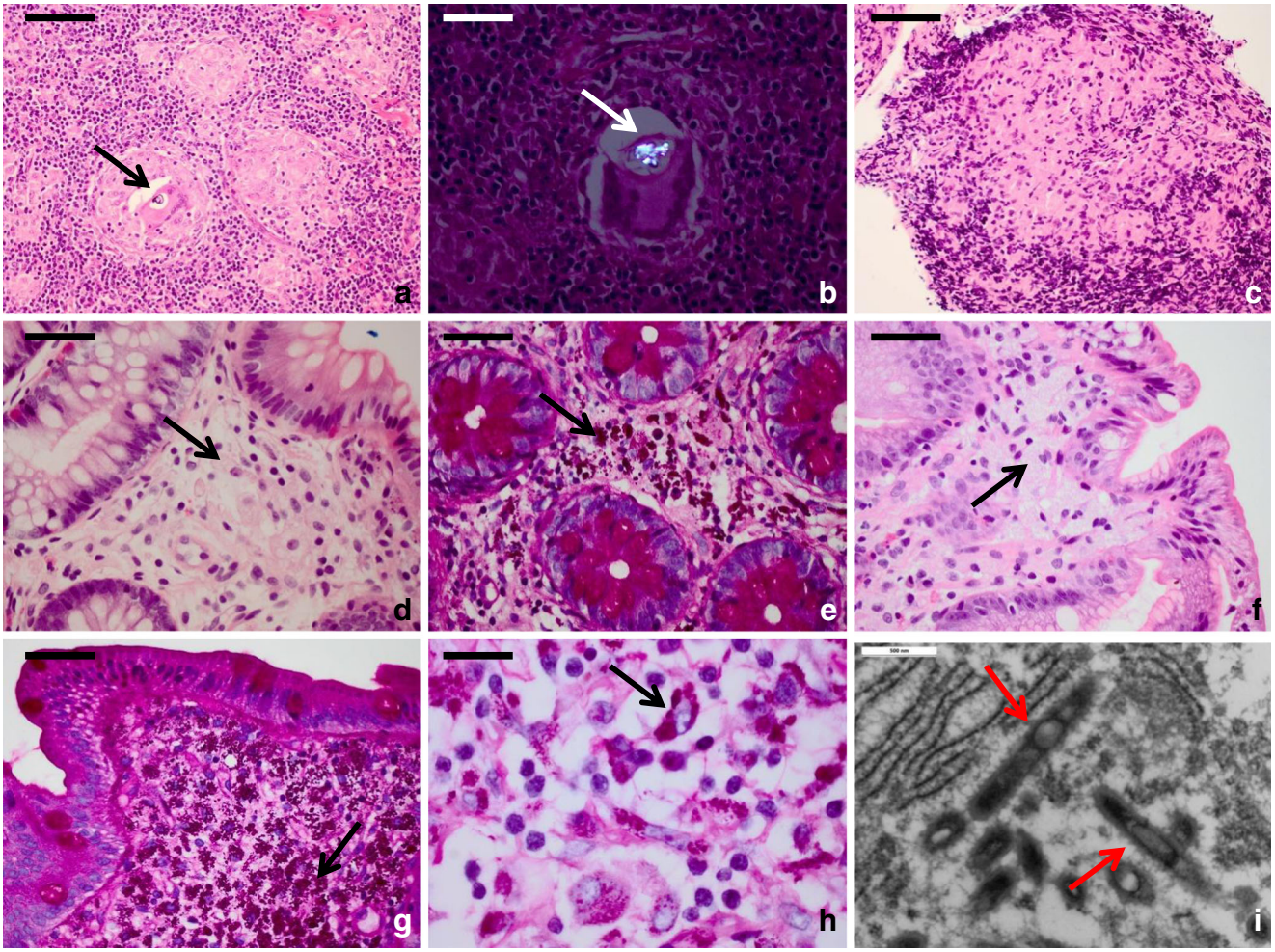

Fig. 1 **a** Hematoxylin and eosin (HE) staining of a lymph node biopsy with non-caseating epithelioid granulomas (*black arrow*) containing a Schaumann body (*scale bar* 100 μm; original magnification ×200). **b** Calcium oxalate crystals (*white arrow*) in an epithelioid granuloma in a lymph node biopsy upon polarized light microscopy (*scale bar* 50 μm; original magnification ×400). **c** HE staining of an ileal biopsy with an epithelioid non-caseating granuloma in the mucosa (*scale bar* 100 μm; original magnification ×200). **d** HE staining of a caecal biopsy, with numerous foamy macrophages in the lamina propria (*black arrow*, *scale bar* 50 μm; original magnification ×400). **e** Periodic acid-Schiff (PAS) staining shows numerous PAS-positive macrophages in the lamina propria of the caecum (*black arrow*, *scale bar* 50 μm; original magnification ×400). **f** HE staining of a duodenal biopsy, with numerous foamy macrophages in the lamina propria (*black arrow*, *scale bar* 50 μm; original magnification ×400). **g** PAS staining shows accumulation of PAS-positive macrophages in the lamina propria of the duodenum (*black arrow*, *scale bar* 50 μm; original magnification ×400). **h** PAS staining confirms the focal presence of PAS-positive macrophages in the second lymph node biopsy (*black arrow*, *scale bar* 20 μm; original magnification ×1000). **i** Electron microscopy confirms the focal presence of intracellular rod-shaped bacilli in macrophages in the second cervical lymph node biopsy (*red arrows*, *scale bar* 500 nm, original magnification ×30,000)

In February 2016, the man was referred to the University Hospital of Ghent. Upon referral, clinical examination confirmed the cervical lymphadenopathy. There was no splenomegaly or hepatomegaly. He had no respiratory or gastrointestinal symptoms. Blood tests showed an iron-deficiency anemia. A Mantoux test was negative. CT of the thorax and abdomen showed extensive infradiaphragmatic, mediastinal, and cervical lymphadenopathy. A new biopsy of a cervical lymph node was performed, since a lymphoma was suspected. Again, the biopsy showed numerous epithelioid non-caseating granulomas, without any evidence for lymphoma. Subsequent PET-CT showed numerous PET-positive lymph nodes above and below the diaphragm, as well as increased FDG uptake in the stomach, ileum, and caecum. Therefore, gastroduodenoscopy and ileocolonoscopy were performed. Ileal biopsies showed focal epithelioid granulomas (Fig. 1c). Biopsies of the duodenal and colon mucosa showed accumulation of foamy macrophages in the lamina propria (Fig. 1d–g). Periodic acid-Schiff (PAS) staining showed numerous diastase-resistant PAS-positive particles in the macrophages (Fig. 1e, g). The diagnosis of Whipple's disease was finally established.

Subsequent transesophageal echocardiography showed endocarditis of the mitral and tricuspid valve. Polymerase chain

reaction (PCR) revealed the presence of *T. whipplei* in cerebrospinal fluid. The patient was initially treated with intravenous ceftriaxone for 4 weeks, after which a combination of trimethoprim, doxycycline, and hydroxychloroquine was prescribed for at least 1 year. After 1 day, trimethoprim was stopped because the patient developed a rash. When last seen in August 2016, the patient's condition had significantly improved and he was free of symptoms.

Retrospectively, DNA was extracted from the lymph node biopsies from January 2013 and March 2016. PCR for *T. whipplei* was performed at a reference laboratory (OLV Hospital Aalst, Aalst, Belgium) and was positive in both lymph node biopsies. Apparently, the patient already had Whipple's disease in 2013, which was initially diagnosed as sarcoidosis. Retrospectively, PAS staining revealed focal presence of PAS-positive granules in the macrophages of the second lymph node biopsy of 2016 (Fig. 1h), but not in the first lymph node biopsy of 2013. Examination with electron microscopy confirmed the focal presence of rod-shaped bacilli in the second lymph node biopsy (Fig. 1i), but not in the first lymph node biopsy.

Discussion

This case report highlights the challenge in diagnosing Whipple's disease and emphasizes numerous (histopathological) diagnostic pitfalls, since many other conditions can mimic its course. The initial presentation of this patient was misleading, as there were no gastrointestinal symptoms. Although the classic form of Whipple's disease is characterized by diarrhea, abdominal pain, and weight loss due to malabsorption, these symptoms can be preceded by prolonged migratory arthralgia, and atypical prodromi have been described [10]. Many patients with Whipple's disease develop lymphadenopathies during the course of their disease, but these can be observed in many other conditions, such as sarcoidosis. Sarcoidosis is a systemic disease, characterized by varying pulmonary symptoms and granulomatous lymphadenopathy [11]. Granulomas are thought to arise because macrophages are unable to degrade a yet unknown causative agent [11]. Alternative diseases, such as mycobacterial infections, need to be excluded before a diagnosis of sarcoidosis is established. The presence of numerous epithelioid non-necrotising granulomas in the cervical lymph nodes of this patient lead to an initial tentative diagnosis of sarcoidosis. Because of its low incidence and the absence of gastrointestinal symptoms, Whipple's disease was not considered at first.

Sarcoidosis is a rare mimicker of Whipple's disease. In 1993, Rouillon et al. reported a woman diagnosed with inflammatory rheumatism and sarcoidosis, who was eventually shown to have Whipple's disease [8]. Similar to our patient, the diagnosis of sarcoidosis was established following a biopsy of a cervical lymph node, showing epithelioid granulomas without caseous necrosis. Unlike our patient, she initially presented with mere arthralgia, and she only developed intermittent fever and enlarged lymph nodes in a later stage of her disease [8].

Our patient did not only have granulomas in the cervical lymph nodes (Fig. 1a), but in the ileal mucosa as well (Fig. 1c). This finding, together with the clinical information on migratory arthralgia, could have misled us to diagnose Crohn's ileitis combined with spondyloarthropathy. A similar misdiagnosis has been reported before [7]. However, the presence of numerous foamy macrophages in the lamina propria of the caecum pointed towards another pathologic condition. Macrophages can obtain a foamy aspect due to the storage of mucins, lipids, abnormal metabolites, or microorganisms [9]. PAS-positive diastase-resistant granules in macrophages in the colon can be observed in many infectious conditions, such as (atypical) mycobacterial infection, histoplasmosis, and visceral leishmaniasis [9]. A similar histopathological pattern can be observed in Whipple's disease, although involvement of the colon is considered to be an extremely rare event [4, 9]. We assume that the massive presence of PAS-positive macrophages in the lamina propria of the colon represents a late stage of disease. This was also suggested by the extent of disease in our patient, illustrated by the presence of cardiac valvular disease and asymptomatic involvement of the central nervous system (CNS). Asymptomatic presence of *T. whipplei* in the cerebrospinal fluid has been reported in up to 50% of patients and needs to be excluded by PCR [5]. CNS involvement requires treatment with antibiotics that pass the blood-brain barrier and reach high concentrations in the cerebrospinal fluid, such as ceftriaxone [10].

The danger of misdiagnosis lies in the subsequent mistreatment of the patient, especially when a diagnosis of sarcoidosis is established. The mainstay of sarcoidosis treatment is immunosuppressive treatment with corticosteroids [11]. Patients with Whipple's disease, who are inadvertently treated with immunosuppressive therapies before being treated with antibiotics, are at risk of developing immune reconstitution inflammatory syndrome (IRIS) at the moment they have received antibiotics. IRIS is marked by recurrent symptoms of Whipple's disease after initial response to antibiotic therapy. It is a frequently observed complication in patients who have initially been treated with immunosuppressive therapy because of an assumed diagnosis of sarcoidosis or a rheumatic disease, before a diagnosis of Whipple's disease was established [5]. If Whipple's disease is not recognized in time, it can cause major complications such as endocarditis and CNS manifestations [2, 5]. If left untreated, the disease is fatal.

In summary, we reported a patient with an atypical presentation of Whipple's disease. Based on the obtained histopathological images, we discussed potential mimics of Whipple's disease, such as sarcoidosis, several macrophage-related

diseases of the gut, and Crohn's ileitis with spondyloarthropathy. As the history of this patient shows, extra-intestinal symptoms such as granulomatous lymphadenopathy can precede gastrointestinal manifestation of Whipple's disease for many years. Despite its rare prevalence, we believe that Whipple's disease should be included in the differential diagnosis when sarcoidosis is considered, even in the absence of gastrointestinal symptoms. We recommend exclusion of Whipple's disease by duodenal biopsy before immunosuppressive therapy for sarcoidosis is administered. In addition, Whipple's disease can be diagnosed by performing PCR on DNA extracted from a lymph node biopsy containing granulomas, as was the case in the patient reported here.

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