Case report

Secondary immune thrombocytopenia (ITP) as an initial presentation of Whipple's disease

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ABSTRACT

Immune thrombocytopenia (ITP) is a heterogeneous autoimmune disease characterized by low platelet count that has been associated with a number of chronic infections but rarely described as a manifestation of Whipple's disease (WD). We present a case of Whipple's disease in a patient initially diagnosed with ITP.

A 46-year old male in the fifth decade of life presented with presumed idiopathic ITP and was treated with several therapies including corticosteroids, rituximab, and thrombopoietin receptor agonists. Several years later, he developed weight loss and worsening arthralgias. He was found to have evidence of WD in a jejunal lymph node, the duodenum, and the cerebral spinal fluid (CSF). His diagnosis of WD, as a cause of secondary ITP, came a full 8 years after he was discovered to have thrombocytopenia and over 4 years after he was diagnosed with ITP.

WD is an uncommon, multiorgan system disease caused by the actinomycete *Tropheryma whipplei*. Whipple's disease presents a diagnostic challenge due to the wide array of possible presenting clinical manifestations, as well as a prolonged time course with separation of symptoms over many years. While *T. whipplei* is ubiquitous in the environment, few individuals develop clinical disease, raising the prospect that select immunodeficiencies, both singular or in combination, may play a role in infection.

While rare, in the appropriate clinical setting, one should consider infection with *T. whipplei* in addition to other chronic infections as a cause of secondary ITP regardless of how long ago the diagnosis of ITP was made.

Introduction

Whipple's disease (WD) is an uncommon, multiorgan system disease with a reported annual incidence of approximately 1 per 1,000,000 [1]. It is caused by the actinomycete *Tropheryma whipplei*, which accumulates in multiple host tissues leading to an array of clinical signs and symptoms. WD presents significant diagnostic challenges because of the broad range of potentially affected organ systems as well as its prolonged clinical course; with signs and symptoms often separated by years. Clinical symptoms may include: polyarthritis, weight loss, abdominal pain, steatorrhea, chronic diarrhea, lymphadenopathy, mental status changes, dementia and other central nervous system manifestations, ophthalmologic signs such as uveitis and retinitis, as well as cardiovascular manifestations including endocarditis [1].

Immune thrombocytopenia (ITP) is a heterogeneous autoimmune disease, characterized by low platelet count, associated with several mechanisms including the production of anti-platelet autoantibodies, platelet cytotoxicity induced by T-cells, and failure of megakaryocyte maturation [2]. While many ITP cases are considered idiopathic, secondary cases of ITP are associated with numerous chronic infections including: *Helicobacter pylori*, varicella zoster virus (VZV), hepatitis C virus (HCV), cytomegalovirus (CMV), and human immunodeficiency virus (HIV) [3].

We report a case of WD affecting multiple organ systems with an initial remote presentation of ITP.

Case report

A previously healthy 46-year-old Caucasian male presented to the outpatient oncology clinic of Novant Health Oncology Specialists for an evaluation of immune thrombocytopenia (ITP) in September of 2016. He stated that he had a history of easy bruising and had been told that he had low platelets dating back to 2008. He was diagnosed with ITP in 2012 at another facility when he presented there with a platelet count of approximately 1 (thou/mcL). His initial therapy for ITP consisted of corticosteroids (prednisone and pulse dose dexamethasone). Despite an initial response to corticosteroid therapy, his platelets again fell to less than 10 (thou/mcL) and in September of 2012, he received two 1000 mg intravenous doses of rituximab separated by 14 days and was initiated on romiplostim therapy, resulting in a rise in his platelet count to > 150 (thou/mcL). He subsequently developed diffuse, intermittent arthralgias thought to be related to romiplostim and his therapy was changed to eltrombopag in June of 2013. This was maintained for several years and he occasionally was given additional courses of rituximab when his platelet count declined, including receiving two 1000 mg doses in 2013 and three 1000 mg doses in 2015.

In 2016, he developed worsening fatigue and malaise, persistent arthralgias, as well as weight loss of 82 lbs. He sought care at our institution and in December of 2016 was found to have a white blood cell count of 25.1 (thou/mcL), hemoglobin of 12.2 (gm/dL), and platelet count of 726 (thou/mcL). He denied additional gastrointestinal symptoms. Bone marrow biopsy was performed and showed hypercellular marrow with left-shifted myeloid hyperplasia, negative for lymphoma or acute leukemia. Positive emission tomography (PET) scan revealed hypermetabolic mesenteric and retroperitoneal lymphadenopathy with the largest mesenteric node measuring 4 × 2 centimeters (cm) and standardized uptake value (SUV) max of up to 5. His eltrombopag was discontinued and he underwent therapeutic laparoscopic splenectomy for ITP with biopsy of a jejunal mesenteric lymph node due to concerns that he could have lymphoma. Histologic examination of the spleen was benign; however, the enlarged mesenteric lymph node was found to have foamy histiocytes and scattered acute inflammation (Fig. 1A). These samples were negative for malignancy. Molecular detection, polymerase chain reaction (PCR) for *Tropheryma whipplei* was performed (Mayo Clinic Laboratories, Rochester, Minnesota) and was positive.

Upper gastrointestinal endoscopy was performed and grossly revealed a normal esophagus, stomach and duodenum. Mucosal biopsy of the duodenum demonstrated extensive infiltration of the lamina propria by foamy histiocytes and periodic acid-Schiff diastase (PAS-D) stain demonstrated strong positivity within histiocytes (Fig. 1B,C). Lumbar puncture revealed a cerebrospinal fluid (CSF) white blood cell count of 0, and red blood cell count of 1. CSF protein was 17 (mg/dL) and CSF glucose was 57 (mg/dL). CSF *Tropheryma whipplei* by PCR was positive (ARUP laboratories, Salt Lake City, Utah). Transthoracic echocardiogram was performed and showed no valvular disease.

Initial antimicrobial therapy consisted of a 28-day course of intravenous ceftriaxone, 2 g daily. This was followed by oral trimethoprim-sulfamethoxazole, 1 double strength tablet by mouth twice daily. The patient subjectively reported significant improvement in fatigue, malaise, and diffuse arthralgias. Follow-up laboratory work revealed WBC 18.8 (thou/mcL), hemoglobin 14.8 (thou/mcL), and platelets 188 (thou/mcL).

Discussion

Whipple's disease presents a diagnostic challenge due to the wide array of possible presenting clinical manifestations, as well as a prolonged time course with separation of symptoms over many years. The disease disproportionately affects Caucasian males in the fifth and sixth decades of life [1]. The classic symptoms of Whipple's disease have included involvement of the gastrointestinal tract, central nervous
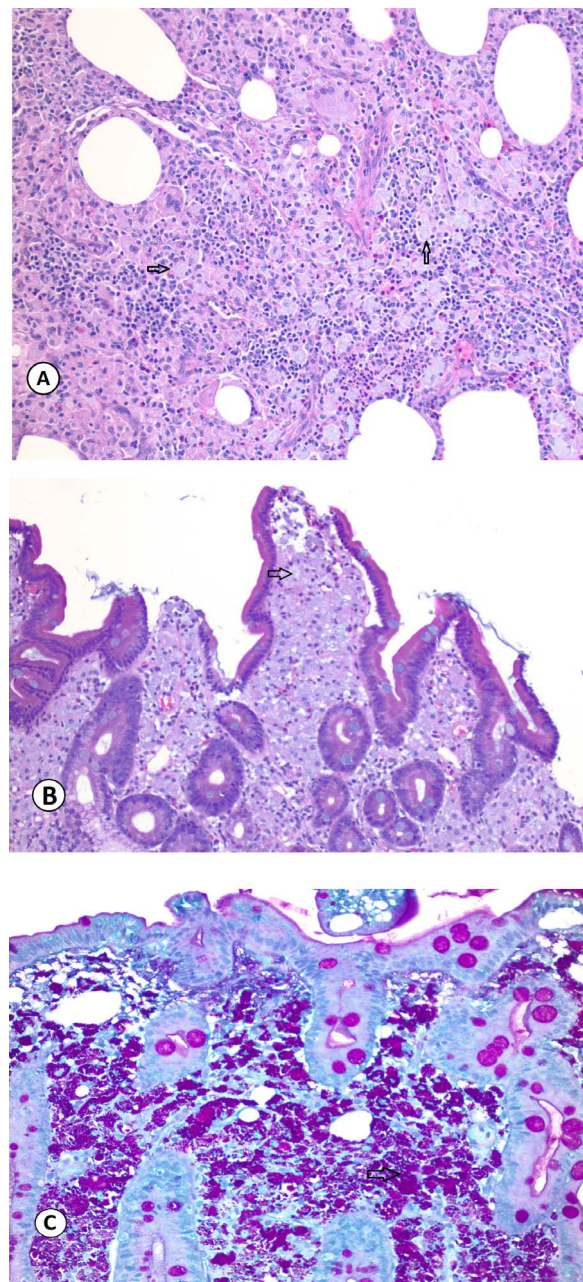

Fig. 1. (A) Hematoxylin and eosin (H & E) stain of lymph node biopsy showing foamy histiocytes (arrows) and scattered acute inflammation. (B) H & E stain of duodenal mucosa biopsy with marked infiltration of the lamina propria with foamy histiocytes (arrow). (C) Periodic acid-Schiff with diastase (PAS-D) stain of duodenal mucosa biopsy showing strong positivity within histiocytes (arrow).

system, lymphatics and joints. Anemia has also been described in up to 85% of patients [1], however, descriptions of thrombocytopenia are less common. A case of Whipple's endocarditis with thrombocytopenia [4] has been described as well as a case of pancytopenia with splenomegaly [5] and pancytopenia caused by bone marrow invasion by *T. whipplei* [6]. Rare case reports in the literature have included a patient with thrombocytopenia and hemolytic anemia as well as a case of ITP diagnosed with WD within one year of ITP diagnosis [7,8].

We present a case of Whipple's disease in a Caucasian male in the fifth decade of life with evidence of disease found in a jejunal lymph node, the duodenum, and the CSF. He initially presented with presumed idiopathic ITP and was treated with several therapies including corticosteroids, rituximab, and thrombopoietin receptor agonists. What is interesting here is that his diagnosis of WD, as a cause of secondary ITP,

came a full 8 years after he was discovered to have thrombocytopenia and over 4 years after he was diagnosed with ITP. In addition, while he did develop weight loss, he did not have additional gastrointestinal manifestations such as diarrhea and steatorrhea, even after treatment with corticosteroids. Corticosteroids have been implicated as a precipitator of diarrhea in individuals chronically infected with *T. whipplei* [9].

While *T. whipplei* is ubiquitous in the environment, few individuals develop clinical disease, raising the prospect that select immunodeficiencies, both singular or in combination, may play a role in infection. Individuals with WD often have large bacterial burdens without evidence of vigorous immune response. The observed immune system characteristics in patients with WD have included altered cytokine production, impairment of monocyte and macrophage function in the small bowel, impaired T-helper cell function, and alterations in immunoglobulin levels [9,10]. While it has been suggested that immunoglobin ratio may be diagnostically helpful in WD [9], the subtle immunodeficiencies associated with WD are difficult to recognize in most clinical settings and immunoglobulin levels were not obtained in this case. It has also been shown that the addition of immunomodulating agents including corticosteroids and tumor necrosis factor alpha therapies may accelerate WD progression [9,11]. The addition of these therapies can increase immunosuppression in individuals who already have baseline immune system dysfunction and, if infected with *T. whipplei*, make clinical disease more apparent [9]. This patient did receive rituximab, a CD20 monoclonal antibody that targets antigens on the surface of lymphocytes. Both B lymphocytes, and to a lesser extent T lymphocytes, express CD20 antigens so rituximab has the potential to affect multiple cell lines [12,13]. However, it is unclear what role, if any, rituximab played in this case or whether the effect of rituximab on B lymphocytes or small populations of T lymphocytes would increase the risk of progression of WD. Rituximab was given to a patient subsequently diagnosed with WD in one case series but the patient had also received multiple additional biologic therapies [14].

While rare, in the appropriate clinical setting, one should consider infection with *T. whipplei* in addition to other chronic infections as a cause of secondary ITP regardless of how long ago the diagnosis of ITP was made.

Conflict of interest

All authors: No reported conflicts.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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