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Case Report

Tics and Tumors, A Case Report of Babesiosis and IgG4 Retroperitoneal Fibrosis

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ARTICLE INFO

Article history:

Received: 21 October, 2019

Accepted: 14 November, 2019

Published: 27 November, 2019

Keywords:

Babesiosis

retroperitoneal fibrosis

tamoxifen

rituximab

IgG-4

ureteral compression

ABSTRACT

Retroperitoneal fibrosis (RPF) is a rare fibroinflammatory tumor of the retroperitoneum thought to be due to either idiopathic disease or related to underlying malignancy. Recently idiopathic RPF has been reclassified as an immune mediated IgG-4 related disease. When left unchecked, RPF often progresses, leading to compression of retroperitoneal structures and complete ureteral obstruction. Babesiosis is an intraerythrocytic parasitic disease that has demonstrated an *in vitro* association with increased IgG-4 levels. Both diseases are insidious, presenting with symptoms commonly identified as a viral prodrome, including malaise and fatigue. Within we present a case of a 68-year-old African American farmer with recent tick exposure who presented with symptoms of malaise, weight loss, elevated creatinine and new retroperitoneal mass. Serum testing revealed recent Babesiosis exposure, and biopsy revealed new onset retroperitoneal fibrosis. Once treated for babesiosis, the patient's disease ceased its progression, and he remains on treatment with tamoxifen and stable disease. Further research of the *in vivo* association of babesiosis and IgG-4 related disease is needed.

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Case Report

A 68-year-old African American male with a past medical history of hypertension, hyperlipidemia, type II diabetes mellitus, and treated borreliosis presented to his primary care physician with nasal congestion, cough, malaise and 18kg of unintentional weight loss. The patient had no family history of malignancy, worked regularly as a farmer, and his daily medication regimen consisted of metformin 500mg twice a day, pravastatin 40mg and lisinopril 10mg once a day. During this visit the patient was started on doxycycline 100mg twice daily for 3 weeks for an unspecified skin rash the patient described a week prior. Over the next three months the patient's creatinine elevated from a baseline of 1.0mg/dL (reference range [RR] 0.6 - 1.3 mg/dL) to 2.1mg/dl and the patient's appetite and weight loss continued to worsen. At that time an abdominal ultrasound revealed a heterogeneous retroperitoneal density displacing the right kidney without hydronephrosis. Although the patient's elevated creatinine precluded IV contrast use, a computerized tomography scan without contrast of the abdomen

revealed an enlarged irregular right kidney with ill-defined lower borders, and a soft tissue density measuring 8.0x9.2cm extending along the inferior pole of the right kidney to both the psoas muscle and common iliac muscles. Magnetic resonance imaging showed the mass to be retroperitoneal, engulfing the right kidney and compressing the inferior vena cava. Immunology testing was sent which revealed the presence of new *Babesia microti* IgG 1:160 (RR <1:10) as well as titers indicating past borreliosis infection (Table 1). The patient was prescribed 10 days of azithromycin with an initial dose of 1000mg followed by 9 days of 250mg as well as atovaquone 750mg twice daily for 10 days. Multiple needle biopsies were taken of the soft tissue density which revealed soft tissue fibrosis and a mixed inflammatory pattern of lymphocytes, plasma cells and eosinophils without stigmata of lymphoma or sarcoma. IgG immunostaining revealed positive IgG4 plasma cells. Flow cytometry revealed a mixed lymphocyte population without monotypic B cells, 27% mononuclear cells (expressing CD45), 13% T cells with a CD4:8 ratio of 9:1, 11% B cells (with a majority positive of FMC-7 and CD22, with partial expression of CD23). Both a subset of B and T cells tested positive for CD38, and natural killer cells

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were mildly increased at 6%. The patient was diagnosed with retroperitoneal fibrosis and tamoxifen was started. Eighteen months after his initial diagnosis, the patient's creatinine remained elevated, however his retroperitoneal fibrosis had ceased the initial progression seen on CT imaging. He was continued on tamoxifen with stabilization of his disease.

Discussion

First described in 1948 by Dr. John Ormond, retroperitoneal fibrosis (RPF) is a fibroinflammatory tumor of the retroperitoneum typically affecting the perivascular areas around the aorta, common iliac vessels, renal arteries and ureters [1, 2]. RPF is insidious, with initial symptoms that consist of malaise and abdominal pain, otherwise similar to many viral prodromes [3]. When RPF progresses unchecked it often leads to complete ureteral obstruction and compression of the retroperitoneal structures. RPF is a rare disease, with a current known incidence of 1.38 per 100,000 people, however, is likely underdiagnosed due to late symptom onset [3]. Average age of diagnosis is 56, and 69% of those diagnosed with RPF are male [4]. Diagnosis of RPF remains difficult, as no definitive serum-based tests are currently available. Over 60% of patients with RPF present with elevated creatinine due to ureteral compression from retroperitoneal mass, with an average creatinine of 5.6 mg/dL (RR 0.6 - 1.3 mg/dL). Histopathology remains the diagnostic standard for RPF, and tissue samples often demonstrate eosinophilia, lymphoplasmacytic infiltrate, storiform fibrosis as well as obliterative phlebitis [5].

Historically, RPF was either attributed to idiopathic disease or as a result of previous malignancy [2]. However, new studies have suggested that approximately 60% of idiopathic RPF is due to IgG-4 related disease and is now considered a member of the IgG4 related disease category, defined as an immune mediated systemic disease [6-8]. The specific criteria of IgG4 related disease include localized swelling or mass, elevated IgG4 concentration (>135mg/dL), and histopathology demonstrating lymphocytic and plasmocytic infiltration and fibrosis [9]. Treatment regimens for RPF have previously consisted of long-term glucocorticoids, typically oral prednisone with doses ranging from 10 to 75mg per day initial with a long tapering period [4]. However chronic steroid treatment regimens have been associated with immunosuppression, fluid retention, weight gain, hyperglycemia, and psychosis- creating a challenging treatment course due to significant side effects and complications [4]. A systemic review demonstrated that glucocorticoid monotherapy in IgG4-RD demonstrated a 97% initial therapeutic response, however relapse occurred in 33% of patients [10]. Second line treatments for IgG4-RPF have included mofetil, methotrexate and azathioprine [4, 11]. Recently however two alternate regimens have emerged that spare patients from the toxicity of long-term glucocorticoid usage- tamoxifen and rituximab.

Tamoxifen is an oral aromatase inhibitor, a prodrug metabolized to afimoxifene and endoxifen which bind the estrogen receptor with far greater affinity than endogenous estrogen. A study of 118 patients found that although there was greater initial improvement in creatinine and mass regression with glucocorticoids (84% with steroids, vs. 68.3% with tamoxifen), definitive treatment outcomes were not different. However, patients with initial treatment success with tamoxifen were less likely to

have recurrence (21.4% with tamoxifen, vs. 62.5% recurrence with steroids). A later study further evaluated 31 cases of RPF with an associated 44 cases of hydronephrosis on tamoxifen for an average of 13.3 months. Through the course of this treatment, 71% of patients had disease regression and 27/44 stents were removed. Approximately 20% of patients stopped tamoxifen therapy due to side effects or treatment failure, which is comparable to the population treated with glucocorticoids, validating Tamoxifen as a potential alternate therapy [12]. Rituximab is an anti-CD20 antibody, and was evaluated for treatment of RPF at 1,000mg dosed once biweekly for two doses and resulted in disease regression in 97% of participants. Approximately, 47% of patients were in total disease remission at 6 months and 40% at 12 months [13]. A further study retroactively compared rituximab to glucocorticoid treatment and found that although rituximab carries risks for myelosuppression, immunosuppression, hepatotoxicity and neuropathy that rituximab monotherapy was concluded to provide a means of steroid sparing treatment with maintenance of remission and improvement in renal function [4, 14].

Babesiosis, is an intraerythrocytic parasitic disease of the phylum Apicomplexa, the same phyla of malaria (*Plasmodium*), toxoplasmosis (*Toxoplasma gondii*) as well as cryptosporidiosis (*Cryptosporidium*) [15]. The most common vector of human babesiosis is the tick, *Ixodes scapularis* and in eastern North America the animal reservoir is the white-footed mouse *Peromyscus leucopus* [15]. The symptoms of Babesia typically consist of mild illness, malaise and fatigue, followed by inconsistent fever, athermalgia and myalgia [15]. Symptoms can last for several weeks to months, with recovery that can take up to one year [15]. However, not all Babesiosis is mild, and disease can be associated with severe respiratory failure, disseminated intravascular coagulation, liver failure, renal failure and splenic infarction [16]. Babesiosis is not a nationally reportable disease and likely largely underreported as its symptoms are non-specific and easily mistaken for viral illness [17]. Some epidemiologic studies have placed Babesiosis's incidence as similar to gonorrhea, placing its health burden as moderately common or 280 cases per 100,000 [15]. Babesia's life cycle is complicated, with an asexual reproductive phase inside mammalian host erythrocytes and a sexual reproductive phase within the arthropod vector [15]. Within erythrocytes, Babesia trophozoites reproduce via budding, and undergo two successive divisions giving rise to the merozoite tetrad, forming the pathognomonic Maltese cross [15]. In turn, this Maltese cross lyses the erythrocyte during egress and invades nearby erythrocytes. When Babesia infected erythrocytes are imbibed by arthropods they lyse, form ookinetes, and transverse to the arthropods salivary glands where they transform to sporoblasts that remain dormant until the next arthropod feeding. During feedings these sporoblasts can release as many as 10,000 sporozoites for each activated sporoblast in the salivary tissue [15]. Interestingly, each of the tick's life cycles, from larva to nymph and to adult requires an erythrocyte meal from a mammalian host to mature. Subsequently, Babesia relies on tick life cycles for transmission. In summer, hatched larvae infect rodents and advance to the nymph stage. Late spring and summer of the following year, these nymphs transmit Babesia once again before maturing again to adults. Nymphs however are responsible for most of the Babesia transmission [15]. Mild babesiosis has been treated with atovaquone and azithromycin, whereas severe illness with clindamycin, quinine and exchange transfusion [15]. Treatment regimens are widely varied, with case reports of multiple

treatment regimens including a case of cured Babesiosis with artemether, azithromycin, and clindamycin through intramuscular injection and oral intake of atovaquone [18]. There are multiple tests for babesiosis, including serology, blood smears, babesial DNA amplification via PCR, or giemsa stained blood smears [15]. Once a human host has been infected, Babesial DNA persists for an average of 82 days in patients who have not received therapy, and 16 days in patients who received clindamycin and quinine therapy [16]. The length of symptomatic Babesiosis appears dependent on the number of months the patient has been exposed to this foreign DNA. In untreated patients, those with Babesial DNA exposure of less than 3 months were symptomatic for approximately 15 days, but those with DNA exposure over 3 months were symptomatic for 114 days [16].

IgG4 plays a role in both diseases, although that role is yet undefined. The monoclonal anti-IgG4 (clone HP6025; Zymed) antibodies verified to test for Babesiosis, imply that IgG4 is indeed present and in Babesiosis [19]. IgG4 levels have also been used to track responsiveness of RPF IgG4 related disease during treatment courses of rituximab and have been found to be a prognosticating factor [13]. Of interest is the fact that this patient's retroperitoneal fibrosis ceased its ureteral compression and disease progression after treatment of the patient's underlying Babesiosis. After the patient underwent treatment for babesiosis with 10 days of azithromycin (Day 1 1000mg, days 2-9 250mg) as well as atovaquone (750mg twice daily for 10 days) he began tamoxifen therapy and suffered no further disease complications. This association merits further exploration.

Table 1: Initial Immunoassay Values.

Name	Reference range (RR)	Patient's Values
IgG	RR: 700 - 1600 mg/dL	2071 (H)
IgA	RR: 61 - 437 mg/dL	666 (H)
IgM	RR: 20 - 172 mg/dL	62
B Burgdorf 41 Kd (IgG)	No reference range	Present (H)
B Burgdorf 58 Kd (IgG)	No reference range	Present (H)
B Burgdorf 66 Kd (IgG)	No reference range	Present (H)
Babesia microti IgG	Latest Ref Range: Neg:<1:10	1:160 (H)
Babesia microti IgM	Latest Ref Range: Neg:<1:10	<1:10

In conclusion, RPF remains a rare and insidious disease, often presenting with malaise and acute kidney injury from ureteral compression due to the retroperitoneal tumor's mass effect. Babesiosis too is insidious, with symptoms of malaise easily mistaken for a viral prodrome and a diagnosis requiring specialized testing or hematopathologist review. To date, there have been no studies testing for the prevalence of Babesiosis in RPF IgG4 related disease, however studies demonstrating IgG4 as marker for both Babesiosis as well as retroperitoneal fibrosis are intriguing. Furthermore, the concomitant onset of RPF and babesiosis in our patient, as well as cessation of RPF disease progression with

appropriate antibiotic therapy for Babesiosis merits further research. Patient's newly diagnosed with RPF and risk factors for tick exposure in areas endemic with babesiosis should be considered for screening for babesiosis, and if evidence for active babesiosis is found, treatment with azithromycin and atovaquone initiated.

Authors Contribution

M. Adashek, N. Burley, and H. Mannuel completed the background research, drafted and edited the manuscript, and is the grantor of the publication.

Conflicts of Interest

None of the authors have any financial or personal bias to declare.

Funding

None.

Informed Consent

Informed consent was obtained from the patient for educational use of the below mentioned data and no personal patient information has been disclosed. This paper has been written in keeping with the principles of the Declaration of Helsinki.

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