CASE REPORT

Case Report: Ocular toxoplasmosis in a WHIM syndrome immunodeficiency patient [version 1; peer review: 3 approved]

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Abstract

A patient with WHIM syndrome immunodeficiency presented with sudden painless right eye blindness associated with advanced retinal and optic nerve damage. *Toxoplasma gondii* was detected by PCR in vitreous fluid but not serum. The patient was treated with trimethoprim-sulfamethoxazole. Vision did not return; however, the infection did not spread to involve other sites. Toxoplasmosis is rare in primary immunodeficiency disorders and is the first protozoan infection reported in WHIM syndrome.

Keywords

Toxoplasma gondii, Treatment, Retinitis, Optic neuritis, Genetic Immunodeficiency, CXCR4
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Author roles: McDermott DH: Conceptualization, Data Curation, Formal Analysis, Investigation, Writing – Review & Editing; Heusinkveld LE: Data Curation, Writing – Original Draft Preparation, Writing – Review & Editing; Zein WM: Data Curation, Investigation, Methodology, Writing – Review & Editing; Sen HN: Data Curation, Formal Analysis, Investigation, Writing – Review & Editing; Marquesen MM: Investigation, Methodology, Writing – Review & Editing; Parta M: Investigation, Writing – Review & Editing; Rosenzweig SD: Investigation, Methodology, Writing – Review & Editing; Fahle GA: Investigation, Methodology, Writing – Review & Editing; Keller MD: Investigation, Methodology, Supervision, Writing – Review & Editing; Wiley HE: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Resources, Writing – Review & Editing; Murphy PM: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

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Introduction

Toxoplasma gondii is an obligate intracellular protozoan with a wide host range among vertebrates, including humans. Domestic cats and their relatives, the definitive hosts of T. gondii, release large numbers of unsporulated oocysts in their feces, which are then ingested by secondary hosts. Major sources of infection include ingestion of contaminated water or undercooked meat and exposure to other materials contaminated with cat feces, although transmission can also occur by transplantation, blood transfusion and laboratory accidents. Human infection has been estimated to occur in ~30% of individuals worldwide based on seroprevalence studies but usually results in lifelong subclinical infection in immunocompetent individuals. Chronic infection most commonly manifests as tissue cysts in skeletal muscle, myocardium, brain and eye. Acute toxoplasmosis in immunocompetent individuals may present as a mononucleosis-like syndrome. In the setting of acquired immunodeficiency, toxoplasmosis may occur as a result of primary T. gondii acquisition or reactivation of latent infection and may present as systemic illness or as a localized infection. Central nervous system toxoplasmosis is a particular problem in AIDS patients and is an AIDS-defining condition. Ocular toxoplasmosis can also occur in AIDS patients and may even be the presenting manifestation. Vertical transmission of T. gondii is ~40% for women who become infected during pregnancy and may cause severe congenital developmental defects involving the brain, eye and other organs. In the eye, T. gondii may cause a progressive and recurring necrotizing retinochoroiditis and is the most common cause of infectious uveitis worldwide. Optic neuritis is a less frequent presentation that is usually associated with worse visual outcome. Ocular toxoplasmosis occurs in patients with acquired immunodeficiency but has not previously been reported in patients with primary immunodeficiency disorders.

Warts-Hypogammaglobulinemia-Infections-Myelokathexis (WHIM) syndrome is a rare primary immunodeficiency disorder caused by autosomal dominant gain-of-function mutations in the chemokine receptor CXCR4. The primary manifestations of WHIM syndrome are cutaneous and mucosal warts, hypogammaglobulinemia, recurrent non-invasive infections, which are usually bacterial in origin and typically affect the oto-sino-pulmonary tract and skin, and myelokathexis, a term coined for retention of mature neutrophils in bone marrow. Opportunistic and life-threatening infections in WHIM syndrome patients are rare, and significant protozoan infection has not been previously reported.

Clinical course and management

Initial presentation and history

A 14-year-old Hispanic male with WHIM syndrome (mutation CXCR4R334X) from El Salvador presented with painless sudden onset right eye blindness of at least one week’s duration. There was no history of blunt or chemical trauma to the eye, recent bacterial or viral illness, or change in medication, and he reported no eye pain, periorbital swelling, eye discharge, fever, rash or headache. The past medical history was significant for Tetralogy of Fallot which had been repaired surgically. Neutropenia was diagnosed as a neonate, resulting in recurrent upper and lower respiratory tract infections complicated by bronchiectasis and tympanic membrane perforation. He received filgrastim (G-CSF, Amgen) from ages 1–3 but this was discontinued due to bone pain. At age 13, he developed dengue fever and three successive episodes of pneumonia, prompting evaluation for primary immunodeficiency. Panleukopenia was documented (ANC 90, AMC 50, ALC 1070, platelets 122,000, CD4+ T cells 365, CD19+ B cells 11 [all per microliter]). Vision was normal. After obtaining informed consent on an NIH IRB-approved protocol for immunodeficiency screening (05-I-0213), genetic testing of a blood sample identified heterozygous CXCR4R334X, the most common WHIM syndrome genotype. Three months later the patient experienced complete vision loss in the right eye but was otherwise asymptomatic.

Diagnosis

The patient appeared well-developed but underweight (BMI = 14.5) with mild scoliosis. Splenomegaly was noted. Classic features of WHIM syndrome were present, including cutaneous warts, hypogammaglobulinemia, and severe panleukopenia (Table 1). A bone marrow biopsy revealed myelokathexis and an AIDS-defining condition. Ocular toxoplasmosis can also occur in AIDS patients and may even be the presenting manifestation. Vertical transmission of T. gondii is ~40% for women who become infected during pregnancy and may cause severe congenital developmental defects involving the brain, eye and other organs. In the eye, T. gondii may cause a progressive and recurring necrotizing retinochoroiditis and is the most common cause of infectious uveitis worldwide. Optic neuritis is a less frequent presentation that is usually associated with worse visual outcome. Ocular toxoplasmosis occurs in patients with acquired immunodeficiency but has not previously been reported in patients with primary immunodeficiency disorders.

Table 1. Hematologic characteristics of the patient upon presentation to NIH. WBC: white blood cells; RBC: red blood cells; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; AMC: absolute monocyte count; NK: natural killer cells. Measured values for the cell counts are cells/µL, except as otherwise noted.

| Characteristic  | Value       | Reference range |
|----------------|-------------|-----------------|
| WBC            | 1060        | 4230–9010       |
| RBC            | 5.04 x 10^6 | 4.62–6.08 x 10^6| |
| Hematocrit (%) | 39.9        | 40.1–51%        |
| Hemoglobin (g/dL) | 13.4      | 13.7–17.5       |
| Platelets      | 1.4 x 10^5  | 1.61–3.47 x 10^5| |
| ANC            | 130         | 1780–5380       |
| ALC            | 880         | 1320–3570       |
| AMC            | 40          | 30–820          |
| Eosinophils    | 10          | 40–540          |
| Basophils      | 10          | 10–80           |
| NK             | 213         | 126–729         |
| NK-T           | 59          | 29–299          |
| CD3+           | 663         | 714–2266        |
| CD4+           | 259         | 359–1565        |
| CD4/CD45RA+    | 4           | 102–1041        |
| CD8+           | 338         | 178–853         |
| CD8/CD45RA+    | 10          | 85–568          |
| CD20+          | 6           | 59–329          |
| IgG (mg/dL)    | 724         | 716–1711        |
| IgM (mg/dL)    | 98          | 15–188          |
| IgA (mg/dL)    | 9           | 47–249          |
| IgE (IU/mL)    | 24.2        | 0–90            |
with an elevated 4:1 myeloid:erythroid ratio. In the right eye, light perception was absent and there was an afferent pupillary defect. Dilated fundus examination showed a pale retina with widespread white subretinal infiltrates with a necrotizing appearance in some areas, patches of subretinal fibrosis, mild vitritis and a fibrotic band reaching the optical nerve head and a pale optic nerve (Figure 1). Spectral domain optical coherence tomography images showed variable hyper-reflective infiltration of the subretinal space throughout the macula without serous subretinal fluid, with disruption of normal lamination of the macula. B-scan ultrasound showed mild vitreous opacities with presence of a posterior hyaloid membrane still adherent to the optic disc, but separated from the retina in other areas posteriorly, with presence of a vitreoschisis cavity inferiorly, without any retinal detachment, and without any definite eye wall thickening or episcleral lucency. The left eye was normal. Cranial CT scan showed mild sinusitis. Filgrastim (1 mcg/kg/day) was given resulting in increased ANC and increased vitritis the next day, suggesting the possibility of an ongoing chronic infection. Peripheral blood cultures were negative. A vitreous biopsy showed mixed inflammatory cells, and PCR testing was positive for *T. gondii* in vitreous fluid but negative in serum and bone marrow. Serum IgG for *T. gondii* was 599 international units/ml. Tests for other viral (CMV, EBV, VZV, HSV, dengue), fungal (Histoplasma, Cryptococcus), bacterial (Bartonella, Rickettsia, Legionella, Mycobacterium) and parasitic (Leishmania, Toxocara) pathogens were negative. A diagnosis of advanced ocular toxoplasmosis with ongoing active lesions was made.

**Treatment and follow-up**

The patient was treated with oral pyrimethamine (75 mg loading dose then 25 mg/day), leucovorin (7.5 mg/day), and sulfadiazine (1500 mg 2x/day) for six weeks. After treatment, chorioretinal scarring appeared stable. Serum IgG for *T. gondii* declined to 222 IU/ml 32 months later. The macula was fibrotic and atrophic without signs of active exudative lesions over 4 years follow up, during which the patient has received daily prophylactic trimethoprim/sulfamethoxazole (800 mg/160 mg). The optic nerve is atrophic in the right eye and normal in the left. Light perception continues to be absent in the right eye but left eye vision has remained normal. He has successfully completed a Phase 3 double blinded clinical trial (ClinicalTrials.gov Identifier NCT02231879) comparing 14 months each of twice daily plerixafor (Sanofi) and filgrastim (Amgen) treatment and is currently receiving open label filgrastim (1 mcg/kg/day). The patient has had markedly improved growth, no significant bacterial infections and is fully active, competing at the national level in equestrian sports.

**Figure 1.** Shown on top are montage fundoscopic images of the patient’s right (OD) and left (OS) eyes at the time of presentation. The lower right panel shows the optical coherence tomography findings at presentation for OD (top) and OS (bottom).
Discussion

To our knowledge, this is the first detailed report of localized ocular toxoplasmosis in a primary immunodeficiency disorder and the first report of a protozoan infection in WHIM syndrome. In addition, optic nerve involvement as seen in our patient is rare in ocular toxoplasmosis (<5%)\(^{1}\).

Although symptomatic toxoplasmosis occurs frequently in the setting of acquired immunodeficiency, especially HIV infection, it is rarely associated with a primary immunodeficiency disorder. Disseminated toxoplasmosis has been reported in several patients with X-linked hyper-IgM (XLH1) syndrome\(^{6,7}\). Neutropenia was observed in two of these patients\(^{8}\). Two patients were receiving IVIg replacement therapy at the time toxoplasmosis was diagnosed\(^{9,10}\), while two others were previously undiagnosed with XLH1 and had untreated hypogammaglobulinemia\(^{11}\). Of note, one patient had been taking trimethoprim/sulfamethoxazole as prophylaxis for recurrent otitis media prior to the onset of symptomatic toxoplasmosis\(^{1}\). Disseminated *T. gondii* infection with ocular manifestations has been reported in a patient with ataxia telangiectasia\(^{12}\). This patient did not have lymphopenia and had received IVIg replacement therapy. In addition, fatal cerebral toxoplasmosis was reported in two patients with common variable immunodeficiency\(^{13}\).

Thus, hypogammaglobulinemia is a common feature of primary immunodeficiency disorders in which toxoplasmosis has been reported, suggesting the importance of antibody-mediated immunity for controlling *T. gondii*. Although our patient had low immunoglobulins, he developed a strong IgG response to *T. gondii*. The quality of the antibodies and the kinetics of the response are unknown but evidently were insufficient to initially control the pathogen. Cell-mediated immunity is also important in control of *T. gondii* infection, with critical complementary roles for monocytes, neutrophils, dendritic cells, plasma cells, and CD4+ and CD8+ T cells\(^{14-16}\). IFN\(\gamma\) and IL-12 are hallmarks of the Th1 response to *T. gondii* infection\(^{14}\). Neutrophils, activated monocytes, macrophages, and dendritic cells all produce IL-12, whereas IFN\(\gamma\) is produced by NK cells, neutrophils, and effector T cells in response to *T. gondii* invasion\(^{13}\).

An explanation for the paucity of symptomatic *T. gondii* infections among patients with primary immunodeficiency is lacking. Possible explanations include the frequent use of broad-spectrum antibiotics such as trimethoprim-sulfamethoxazole for patients with primary and acquired immunodeficiency disorders and environmental precautions taken to limit exposure to pathogens in general.

WHIM syndrome is a complex, phenotypically heterogenous primary immunodeficiency disorder that frequently involves defects in steady state levels of leukocytes and antibody in the blood, as in our patient. Given that the patient has multiple immunologic abnormalities, it is not possible to attribute his susceptibility to *T. gondii* to any single one.

In summary, we describe in detail a very rare case of primary ocular toxoplasmosis in primary immunodeficiency disease and the first case of protozoan infection in WHIM syndrome. The precise immunologic abnormalities among the spectrum of abnormalities resulting from WHIM syndrome that predisposed the patient to such a devastating outcome of *T. gondii* infection is currently unknown.

**Consent**

Written informed pediatric assent was obtained from the patient, and the patient’s mother provided parental written informed consent for the publication of the patient’s clinical details and any associated images.

**Data availability**

All data underlying the results are available as part of the article and no additional source data are required.

**Grant information**

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The Center for Disease Control notes that ‘parasitic infections are typically associated with poor and often marginalized communities in low-income countries. However, these infections are also present in the United States.’ Additionally, they have designated toxoplasmosis a neglected parasitic infection and a public health priority because of the little attention it has received¹. Based on the number of people infected, the severity of illness, and the ability for prevention and treatment, health care providers need to take note of its increasing prevalence along with the common signs and symptoms. The case report by McDermott et al. provides this opportunity.

The report details a teen with a WHIM syndrome, a primary immunodeficiency disorder, who developed sudden painless right eye blindness due to ocular toxoplasmosis (OT) or toxoplasmic chorioretinitis². However, it is unknown whether his infection was congenitally acquired or acquired later in life through contaminated food or water or possibly as a result of a blood transfusion during his Tetralogy of Fallot repair. The maternal prenatal history, birth history, and the timing of his immigration might yield some clues. There is evidence that persons with congenital infection have a higher incidence of macular involvement, as in this case, and therefore, have an increased risk of legal blindness³.

Additionally, testing for IgM and performing a quantitative IgG avidity test may help differentiate acute from chronic infection. The avidity test is based on the immovability antigen and antibody attachment where the IgG antibody binds weakly to the antigen during the initial stage but over weeks or months progressively increases⁴. Patients with positive IgM and/or low IgG avidity are considered as acutely acquired cases (usually defined as acquisition of infection in recent six months. Alternately, a negative IgM and a high IgG avidity index support a more chronic infection. A recent study on immune mediators in the aqueous humor showed that IL-9 and IL-13 were significantly higher in primary OT than in recurrent OT⁶.

Cases of isolated OT commonly results from reactivation of untreated congenital infection which can occur years after birth. However, it also occurs in a small percentage of people with acquired infection, especially in patients that are immunocompromised. This case heightens the awareness of the signs and
symptoms, and consequences of toxoplasmosis infection for healthcare providers. It serves as an opportunity to educate patients, especially in international persons and immunocompromised individuals on common exposures, preventive measures, and treatment.

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Is the background of the case's history and progression described in sufficient detail?
Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
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Université Paris-Saclay, Clamart, France

Is the background of the case's history and progression described in sufficient detail?
David McDermott and colleagues are reporting the first example of protozoan infection (Toxoplasma gondii) in the context of the WHIM syndrome. The patient displays the characteristic clinical features of the syndrome including Human Papillomavirus (HPV)-induced warts, Myelokathexis and severe panleukopenia as detailed in the manuscript. He harbors a well-known CXCR4 mutation (R334X) most likely inherited from one of his parents (although sporadic cases were reported) but this information is not provided. Along this line, whether parents or close relatives also present with serum IgG for T. gondii is likely but not provided. It is interesting to note that the patient developed dengue virus infection one year before being diagnosed for Toxoplasma gondii but was negative for serum IgG (witnessing a primary infection?).

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Diagnostic for Toxoplasma gondii infection and treatment given are clearly mentioned. It would be also interesting that the authors mention about the evolution of Toxoplasma gondii infection by PCR testing during the 4 years follow up in the course of the daily trimethoprim/sulfamethoxazole treatment. The authors mention that infection was detected in vitreous fluid but not in serum nor in bone marrow. Were they other sites tested that would help to better understand the protozoan infection pathogenesis (acquisition/reactivation)? The authors mention that the patient successfully completed phase 3 plerixafor and filgrastim-based clinical trial. It will be thus beneficial for a better understanding of the patient treatment and outcome, to indicate when the patient was enrolled into this trial with regard to the T. gondii 4 year-treatment and, if appropriate, whether any follow up of the infection and responses toward it (e.g. serum Ig) was performed in the course of this trial.

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
As emphasized by David McDermott and colleagues, protozoan infections are rare in primary immunodeficiency disorders and this is first example of such infection in the context of the WHIM syndrome. Authors provide interesting hypotheses that might account for the clinical manifestations of Toxoplasma gondii infection and pathogenic mechanisms. I would recommend them to add recent literature regarding the potential role of CXCR4 in the life cycle of other members of the phylum Apicomplexa (Plasmodium) assessed in rodent models. For other parasites such as helminths (e.g. L. sigmodontis) analyzed in rodent models of infection, neutrophils (and their control by a CXCR4/CXCL12 dependent mechanism) were proposed to be critical elements of the host innate protective response.

Is the case presented with sufficient detail to be useful for other practitioners?
The report of this singular case is of great interest for scientists and clinicians working in the field and certainly very useful for practitioners not well aware of the syndrome.

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Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** HOST/VIRUS interactions with a special interest for the role of chemokine receptors in host surveillance.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Importantly, this case exemplifies that manifestations reported in the acronym “W.H.I.M” (Warts, Hypogammaglobulinemia, Infections and Myelokathexis) insufficiently describe the disease and may even be misleading. Indeed, while the patient clearly presents three of the manifestations emphasized in the acronym 1) Warts 2) a history of recurrent upper and lower respiratory tract Infections and 3) Myelokathexis, the patient does not show biologically defined hypogammaglobulinemia. However, while his IgG levels are in the normal range (according to Table 1), his clinical presentation with repeated respiratory and ENT infections are typical of patients with hypogammaglobulinemia. Furthermore, in the discussion section, the authors suggest that the patient appears to have a qualitative humoral defect. This case clearly demonstrates that the spectrum of WHIM syndrome manifestations range well-beyond the acronym. Importantly, the reader will appreciate that the patient's labs are compatible with combined immunodeficiency: CD4+ T cells 365, CD19+ B cells 11 [per microliter] and very low naive CD4+ and CD8+ T cells.

We can conclude that the authors have given an accurate description of a typical WHIM patient (*CXCR4R334X*) who presents not only well-known manifestations of the disease (neutropenia, warts) as well as lesser known (Tetralogy of Fallot, combined immune deficiency) hallmarks of the disease. This detailed report will greatly help clinicians better apprehend and recognize this complex syndrome in their own patient population.

**Question 2: Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**

The authors describe in detail the challenging diagnosis of toxoplasmic optic neuritis. As a reader, we understand the medical thought-process which led to the diagnosis. Due to the neutropenia, the patient did not initially show strong clinical findings of ocular toxoplasmosis. However, Filgrastim administration unmasked vitritis which is a prominent feature of ocular toxoplasmosis. The diagnosis was then confirmed by PCR testing which was positive for *T. gondii* in vitreous fluid. The patient received standard management of toxoplasmosis-associated optic neuropathy as he was treated with oral pyrimethamine (75 mg loading dose then 25 mg/day), leucovorin (7.5 mg/day), and sulfadiazine (1500 mg 2x/day) for six weeks (Rim Kahloun *et al*, Eye Brain. 2015). Optic neuritis remains an unusual presentation of ocular Toxoplasmosis that is associated with worse visual outcome. This is clearly shown during the prolonged follow-up of the patient who sustains findings of fibrotic and atrophic macula without signs of active exudative lesions.

**Question 3: Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?**

The authors are well aware that rare monogenic diseases such as WHIM syndrome offer a unique window of insight into the role of the CXCR4 pathway in health and disease. In their discussion, the authors offer a brief explanation of the possible pathophysiology of the appearance of toxoplasmic optic neuritis in this WHIM patient. They suggest that he presents with both impaired humoral immunity and defective cell-mediated immunity. In particular, they address the question of a defective IFN-gamma and/or IL-12 pathway in this disease. As of today, there is not a sufficient amount of work in the literature to address this question properly, nevertheless it may have been interesting to cite previous studies such as the work of Laura Tassone *et al* (Blood 2010) which suggested that mature DCs from WHIM patients produce normal amounts of interleukin-12 (p70) compared with the cells derived from healthy donors or
the work of Marinos Kallikourdis et al (blood 2013- figure 5c) in which she shows that IFN-gamma production is not different between CD4⁺ T cells from a healthy donor or a WHIM patient (G336X) activated by anti-CD3– and anti-CD28–coated beads. Clearly, the questions raised by the authors are pertinent and underline the importance of further studies to better characterize the defects in this pathway.

**Question 4: Is the case presented with sufficient detail to be useful for other practitioners?**

WHIM is often classified as a severe congenital neutropenia, which may be misleading to clinicians unfamiliar with the disease. Therefore, this case will be very useful to clinicians involved in the care of patients with WHIM syndrome. This report will remind clinicians that they should keep a high degree of suspicion at all times as it is possible that their WHIM patients may present with unusual infections classically seen in patients with severe T cell immunodeficiency.

**Minor Changes to be addressed:**

Table 1:
- lines for both NK and NK-T are duplicated.
- Patient does not have IgG hypogammaglobulinemia according to reference ranges in table 1. This should be stated in the text.
- It could be useful to bold the values with are outside of the normal range in table 1.

**References**

1. Badolato R, Dotta L, Tassone L, Amendola G, Porta F, Locatelli F, Notarangelo LD, Bertrand Y, Bachelerie F, Donadieu J: Tetralogy of fallot is an uncommon manifestation of warts, hypogammaglobulinemia, infections, and myelokathexis syndrome. *J Pediatr*. 2012; 161 (4): 763-5 PubMed Abstract I Publisher Full Text
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3. Tassone L, Moratto D, Vermi W, De Francesco M, Notarangelo LD, Porta F, Lougaris V, Facchetti F, Plebani A, Badolato R: Defect of plasmacytoid dendritic cells in warts, hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome patients. *Blood*. 2010; 116 (23): 4870-3 PubMed Abstract I Publisher Full Text
4. Kallikourdis M, Trovato AE, Anselmi F, Sarukhan A, Roselli G, Tassone L, Badolato R, Viola A: The CXCR4 mutations in WHIM syndrome impair the stability of the T-cell immunologic synapse. *Blood*. 2013; 122 (5): 666-73 PubMed Abstract I Publisher Full Text

**Is the background of the case's history and progression described in sufficient detail?**

Yes

**Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?**

Yes
Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Primary immune deficiency.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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