Case Report

Toxoplasma causing persistent massive cervical lymphadenopathy in a healthy young male

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Abstract

Toxoplasma, an obligate intracellular pathogen is known to cause fatal infections in the immune-compromised host. Persistent lymphadenopathy is uncommon and may mimic viral lymphadenitis and chronic infections such as tuberculosis or hematological malignancy.

We report a case of a 22 year old student who presented with massive posterior cervical lymphadenopathy. He gave a history of close contact with cats. There were no constitutional symptoms and viral serology for CMV, EBV and HIV came negative although biochemistry and blood picture were compatible with viral infection. A diagnosis of toxoplasmosis was made with positive serology (IgM) and compatible histology showing epithelioid histiocytes forming microgranuloma with preserved lymph node architecture after excluding other etiologies. Initially a conservative approach was adapted but due to non-resolution of lymphadenopathy co- trimoxazole was initiated with a positive response.

Keywords Toxoplasma, cervical lymphadenopathy, co-trimoxazole, serology, microgranuloma

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Introduction

Toxoplasma an obligate intracellular pathogen, usually causes asymptomatic infection in healthy host[1,2]. It can cause fatal infections in immunosuppressed patients. Cervical lymphadenopathy (CL) is a known presentation of toxoplasma infection and can be present in 10-20% of acute cases[2], although a frequently ignored diagnosis by many physicians (3)*Toxoplasma gondii* is a parasite that commonly infects warm blooded animals including humans. The primary host is the feline family. The disease is transmitted via ingestion of infected meat, food water sources contaminated by infected animal feces. Vertical transmission is also commonly described[1,3]

Risk factors for toxoplasma infection include, poor socio-economic status, work with soil related occupations, crowded environment and poor education [2]. Diagnosis in the immunocompetent include serological testing, nevertheless nodal biopsy is often performed due to the initial concerns of lymphoma [7].

CL is commonly due to benign causes including viral infections such as EBV, HIV, hypersensitivity, autoimmune etiologies, sarcoidosis and benign reactive lymphadenopathies such as Kikuchi's disease. More sinister causes of CL include lymphomas and potentially malignant lymphoproliferative diseases such as Castleman's disease and Lymphomatoid granulomatosis[4].

There are reported cases of co-existing toxoplasma and lymphoma [4]and even toxoplasmosis in patients being treated for tuberculosis[2,5]. Thus diagnosis of toxoplasmosis may not be straight forward. Acute toxoplasmosis can be diagnosed by combination of IgM and IgG, although IgM can persist for as long as one year. IgG avidity testing can be used to discriminate between recent and past infections. Other option is for sequential monitoring of toxoplasma antibodies to demonstrate an increasing titer [4]. Historically the triad of florid reactive follicular hyperplasia, clusters of epithelioid histiocytes, and focal sinusoidal distension by monocytoid B cells has been considered to be diagnostic of toxoplasmic lymphadenitis (TL)[6]. A study by Eapen et al, 2005 noted that although highly specific (96.6%) this triad had a sensitivity of only 44.4% the limiting factor being monocytoid B cells. Thus they formulated an evidence based diagnostic criteria for diagnosis of toxoplasma lymphadenopathy with [1] presence of micro-granulomas, [2] lower than grade 2 macro-granuloma, [3] absence of giant cells, and [4] follicular hyperplasia. These criteria seem to have a sensitivity of 100% and a specificity of 96.6% [6].

Treatment of toxoplasmosis is mainly offered for the immunocompromised. The therapeutic efficacy of co-trimoxazole (CTM) for cerebral and ocular toxoplasmosis is well documented. There is no recommended antibiotic regime for those with toxoplasma lymphadenitis (TL). There have been few studies that demonstrated the efficacy of CTM in the treatment of TL in asymptomatic individuals. Treatment was postulated to reduce the duration of disease and limit prolonged antibiotic use[6,7]We report a case of a 22 year old male who presented with isolated gradually progressive posterior cervical lymphadenopathy with no other local cause for lymphadenitis. Toxoplasma IgM levels came positive and excision biopsy of the lymph node revealed focal collections of granuloma consistent with the diagnosis of toxoplasmosis . Patient had a benign course of illness and lymphadenopathy settled after 3 months with co-trimoxazole therapy.

Case report

A 22 year old previously unevaluated student who is a non-smoker from Gampola, a suburb close to Kandy, Sri Lanka, presented with a neck lump in the posterior cervical region for one month duration. He had no recent fever, cough, or dental infections. He had first noted a single swelling over the posterior cervical neck region which was progressively increasing in size, and later noted to have two adjacent swellings with a similar consistency.

He gave no history of weight loss, recurrent infections, nor any nocturnal sweats. He did not give a history of chronic cough, hemoptysis or exposure to tuberculosis. He had dogs and cats at home who were in close contact with him. None of his family members gave a history of similar lymphadenopathy or constitutional symptoms. He gave no history of travel abroad or within Sri Lanka in the recent past.

On examination he was afebrile with normal vitals. There was no evidence of pediculosis or dental caries. There were enlarged non tender focal multiple lymph nodes in the right posterior cervical region, largest approximately 3×3 cm in size and smallest 1×2 cm in size. The lymph nodes had a firm consistency and were not mattered or fixed. The throat was slightly inflamed with enlarged and erythematous left palatine tonsil. There were no other lymph nodes and there was no organomegaly. Ear nose and throat examination excluded any local infections.

Full blood count revealed a normal white cell count of $7.59\times10^3/\mu L$ with lymphocyte predominance: $3.05\times10^9/\mu L$(40%). Eosinophil count was 0.12×109/µL, Hemoglobin was 15.9g/dL and platelets were 333 $\times10^9/\mu L$. His inflammatory markers were normal with an ESR of 1mm/hour and CRP of 4.7mg/L. Liver functions showed slightly elevated transaminases (ALT 175U/L and AST 85.2U/L) normal bilirubin levels with a normal reticulocyte count and LDH. Coagulation profile and renal functions were all in the normal range. Blood picture revealed normocytic normochromic red cells with increased rouleux formation. The white cells showed mild absolute lymphocytosis with atypical lymphocytes with a flowing cytoplasm. Lymphocytes were reactive with no blast cells. Platelets were normal. The picture was suggestive of a viral infection and EBV and CMV serology was suggested for confirmation of

diagnosis. In view of his contact history we sent his toxoplasma serology and proceeded with a lymph node biopsy for confirmation of diagnosis and in view of excluding possible hematological malignancies.

CMV and EBV serologies were negative. Toxoplasma IgM was positive with a negative IgG. Mantoux and sputum samples for AFB came negative. Lymph node biopsy revealed lymph node tissue with relatively preserved architecture. There was reactive follicular hyperplasia with focal collections of epithelioid histiocytes forming small granulomas (Figure 1). These granulomas were seen encroaching the follicular margins in places. Caseous necrosis and suppuration was not seen. Abnormal lymphoid proliferation was not evident. The appearances were in favor of toxoplasmosis according to criteria described in literature. The retroviral screening studies were normal

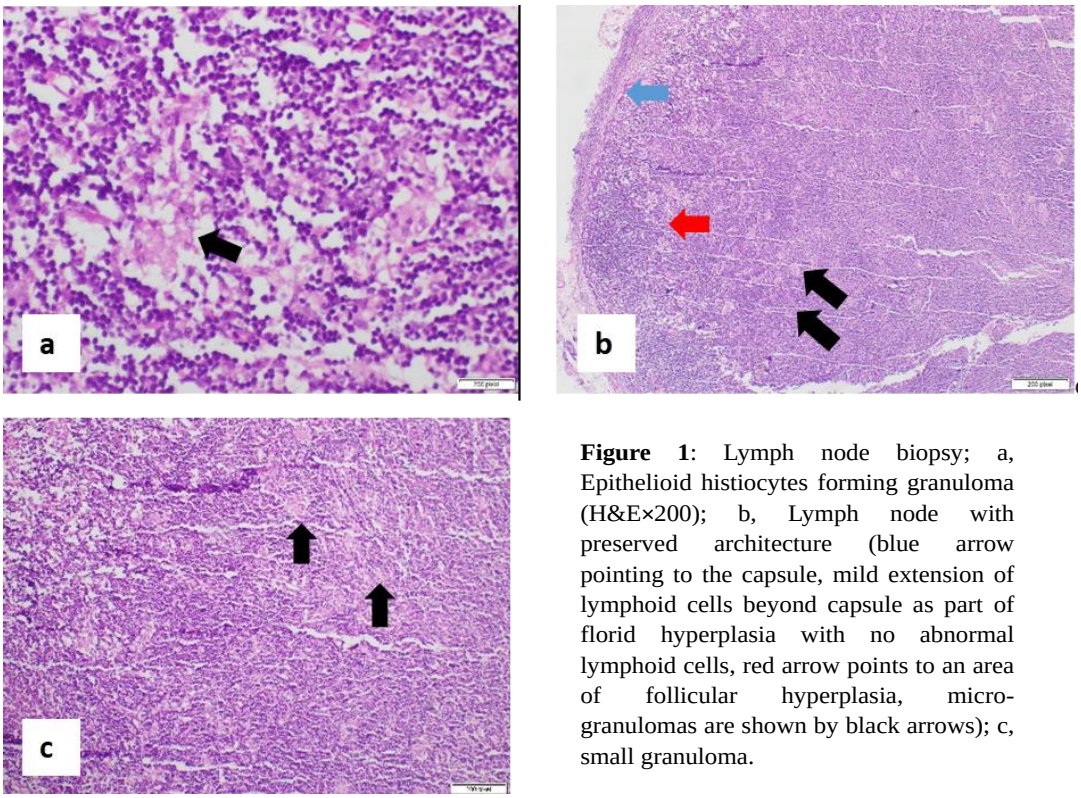

Figure 1: Lymph node biopsy; a, Epithelioid histiocytes forming granuloma (H&E×200); b, Lymph node with preserved architecture (blue arrow pointing to the capsule, mild extension of lymphoid cells beyond capsule as part of florid hyperplasia with no abnormal lymphoid cells, red arrow points to an area of follicular hyperplasia, micro-granulomas are shown by black arrows); c, small granuloma.

Finally a diagnosis of toxoplasmosis was made with the combination of serology and histology. Patient was advised on the benign nature of the infection and the need for proper hygienic food practices. He was managed conservatively discharged after one week with a follow up plan at our medical clinic to observe for resolution of lymphadenopathy.

The lymphadenopathy was persistent after 4 weeks following which we started him on co-trimoxazole (CTM) double strength tablet for one month daily. On the next review his lymphadenopathy was completely resolved.

Discussion

We present a case of massive persistent CL with a diagnosis of toxoplasmosis in a healthy immunocompetent student presenting with throat inflammation and blood picture mimicking viral infection. Resolution of symptoms was only after initiation of specific treatment which is not usually recommended for CL in the setting of toxoplasmosis in the immunocompetent. The case is a representation of diagnostic challenges in toxoplasmosis in a resource poor setting where IgG avidity testing or titers are not available, and diagnosis was via a combination of history, examination, serology, histology and response

to treatment. *Toxoplasma* is known to mimic and may co-exist with many sinister diagnoses such as malignancy autoimmune disease, chronic infections such as TB [2,7,8].Thus a diagnosis should be one of exclusion.

Infection with *T. gondii* is a common non seasonal infection worldwide although it is mostly related to clinically non-significant disease in immune-competent adults [1,3]. The disease typically manifests as isolated asymptomatic cervical lymphadenopathy that resolves within 4 to 6 weeks without treatment. These lymph nodes are typically non tender, discrete isolated and do not suppurate [1]. Although posterior cervical lymphadenopathy is the commonest (10%), suboccipital, supraclavicular, axillary, inguinal, mediastinal, retroperitoneal, and mesenteric node involvement is also described[8,9].

Our patient had an unusually prolonged manifestation of the disease, where the lymphadenopathy lasted for more than 3 months, and was quite large. There was minimal resolution until treatment was initiated.

Lymphadenopathy in toxoplasmosis can resemble infections such as EBV, CMV and at times mimic lymphoma or metastatic carcinoma[4]. There have been cases where co-existence of both lymphoma toxoplasmosis were reported, possibly due to the high prevalence of seropositivity for toxoplasmosis[4]. Our patient's blood picture was consistent with viral infection, thus initially we considered viral lymphadenitis high up in the list of differential diagnoses. Nevertheless patients presenting with fever, sore throat[10], rash and myocarditis mimicking infectious mononucleosis with a final diagnosis of toxoplasma have been reported in literature[7]. There have been cases of disseminated toxoplasma in the immunocompetent as well [7].This is why histological diagnosis with an excision biopsy becomes mandatory in these patients although not necessarily diagnostic[10].

Diagnosis is supported by toxoplasma serology which includes IgM and IgG levels. Acute acquired toxoplasma can be diagnosed by sequential monitoring of serology. Although IgM levels represent acute infection where levels rise within 7 days of infection, reaching a peak around 2-3 months they can persist for up to 1 year following acute infection[8,3]. IgG antibodies detected 1-2 weeks after infection may persist for life. The diagnosis using IgG with avidity testing can differentiate acute and chronic infection, where high avidity antibody excludes infection acquired in the past 3-4 months and low avidity antibodies may last for more than 3 months. Our patient had positive IgM and negative IgG levels. This may indicate acute infection where there is a window period before IgG begins to rise or is too low for detection. But in most cases of toxoplasma both IgM and IgG positivity had been reported, which may not always indicate acute infection. As the patient had close contact with cats, feco-oral route was thought to be the mode of transmission.

Histology has been considered fairly specific in Toxoplasmic lymphadenitis (TL)[10]. Yet the pathologist usually cannot identify organisms in routinely stained tissue sections as complete removal of lymph node with well-preserved architecture is needed for this. Furthermore characteristic nodal architecture may also not be appreciated if samples are not ideal. The gold standard for diagnosis is via direct isolation of the organism from tissue culture, polymerase chain reaction (PCR) or inoculation of mice with infected material. These techniques are neither practical nor feasible in our set up and in many centers worldwide[3]. The classic triad of histology seem to be diagnostic of toxoplasmosis, but there have been efforts to formulate newer more inclusive criteria for better sensitivity and specificity profiles by Eapen et al[6]. Although none of the features are pathognomonic[3], they are useful in cases where other evidence points towards primary toxoplasmosis. But these criteria are still not universally accepted or standardized[6]. Our patient's histology included follicular hyperplasia, micro-granuloma, with no macro-granuloma and presence of epithelioid histiocytes fulfilled all these criteria whilst being consistent with the historic triad of toxoplasma histology. Yet the sections did not show monocytoid B cells, being the limiting factor in our case as well. Furthermore the lymph node architecture was relatively preserved with no abnormal lymphoid cells.

Treatment of toxoplasmosis in immunocompetent individuals is usually not recommended as spontaneous resolution is widely described[3]. But our patient's adenopathy persisted for longer than 3 months and was causing distress to the patient as they were relatively large. There was no consensus on treatment dose, duration or treatment at all for these patients. But few studies have treated these patients with CTM with good effect. The therapeutic effect of the drug on brain and eye infections are well established although not

commonly described with lymphadenopathy. According to literature there have been cases where lymphadenopathy lasts longer than 6 months causing emotional distress and causing antibiotic abuse and misuse. Treatment with co-trimoxazole had limited the disease to one month with good therapeutic effect[11].

Conclusion

CL is a known presentation of *T. gondii*. Nevertheless massive lymphadenopathy lasting for more than one month is unusual. Serology especially IgM may indicate acute infection in the presence of negative IgG, but this occurs at a very short window period during the disease course. In cases of double positive serology IgG titer or avidity testing may be necessary to confirm acute toxoplasmosis. Despite positive serology, histology is necessary to look for classic features of toxoplasma and to exclude sinister differentials as seropositivity is common and can co-exist with other causes of CL. Presence of monocytoid B cells can be the limiting factor in the histological triad, but newer more inclusive criteria although not standardized seem to be more helpful in cases where other possibilities are excluded. Treatment although not usually recommended for TL in immunocompetent individuals, can be considered in distressing persistent lymphadenopathy and can be helpful in confirming the diagnosis while limiting disease duration and antibiotic misuse.

Abbreviations

IgM- Immunoglobulin M; IgG- Immunoglobulin G; LDH- Lactate dehydrogenase; CRP – C-reactive protein; ESR- Erythrocyte sedimentation rate; EBV – Epstein-barr virus; CMV- Cytomegalo virus; CTM/Co-trim- Co-trimoxazole/sulfamethoxazole and trimethoprim; CL- Cervical lymphadenopathy; TL- Toxoplasmic lymphadenitis

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Written informed consent was taken from the patient for publication of this case report.

Availability of data and material: Data generated during this study are included in this published article. All the data are available in the repository of National hospital Kandy,

Authors' contributions: F.N managed the patient, collected the necessary data and drafted the document.SS studied and commented on the pathology samples. FZ conceptualized the case and helped with the draft. SB and KK supervised all the above. All authors read and approved the final manuscript

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