

Toxoplasmic Cervical Lymphadenopathy Precedes Lymphoma

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Abstract

A 35 years old male presented to the outpatient clinic in Alexandria University Hospital with right neck swelling appeared 1 year ago and finally diagnosed, 9 months ago, by histopathologists in the same institute via ultrasound guided FNAC, as Toxoplasmic lymphadenitis. However, the patient represented by sudden increase in the size of this mass 3 months before this re-attendance associated with malaise and low grade fever but there was neither night sweat nor weight loss. The patient had a clear evidence of contact with cats because he was a veterinarian. There was no other positive family, surgical or medical history. On examination, large, firm, mobile right sided lymphadenopathy without signs of active inflammation in the overlying skin at levels III, IV and V. No evident lymph nodes on the other side of the neck or other sites of his body and no hepatosplenomegaly. Temperature and vital signs were normal. ENT examination did not warrant any additional abnormality Erythrocyte Sedimentation Rate (ESR) was 95mm/hr and LDH was 300 U/l these were the first red flag signs that directed the team to further evaluations for Lymphoma. Open surgical biopsy finally diagnosed it as grade III follicular non-Hodgkin's Lymphoma through the Light microscopy which revealed grade III follicular NHL (>15 large centroblasts/high-power field) and DNA analysis which showed t (14; 18) chromosomal translocation characterized by fusion of the bcl-2 gene at 18q21 with the immunoglobulin heavy chain locus at 14q32.

Keywords: Toxoplasmosis; Non-Hodgkin's; Lymphoma; Cytogenetic; Biopsy

Introduction

Toxoplasmosis causes a small but more than 90% of clinical cases with this infection have cervical lymphadenopathy [1] which may persist for months and many patients require biopsy to rule out malignancy [2]; it causes 3 to 7% of cervical lymphadenopathy that requires biopsy [3]. In immunocompetent humans, acquired toxoplasmosis usually gives rise to no symptoms. Some patients have a sore throat with malaise, fever and cervical lymphadenopathy and, on occasion, a patient will present with cervical lymphadenopathy only. Cervical lymph nodes are most commonly involved in Toxoplasmosis followed by axillary lymph nodes [4]. 80 to 90% of asymptomatic toxoplasmic patients have painless cervical lymphadenopathy as the sole manifestation and the remainder of the examination and laboratory workup is almost always normal although the IgM *T. gondii* antibody titer may be high if obtained within a few weeks of the onset of lymphadenopathy [5].

Tissue biopsy is not essential only because of vague symptoms of toxoplasma and absence definitive serological test that confirms toxoplasmosis or excludes malignancy [1], but also because pathologic findings in toxoplasmic L.N are usually diagnostic [4]. In addition, 2% may be diagnosed initially as lymphoma. As well, a small percentage of cases diagnosed initially as toxoplasmosis ultimately prove to be lymphoma and in a few patients the two disorders apparently present simultaneously [6]

Case Representation

A 35 years old male presented to the outpatient clinic in Alexandria University Hospital with right neck swelling appeared 1 year ago and finally diagnosed, 9 months ago, by histopathologists in the same institute via ultrasound guided FNAC, as Toxoplasmic lymphadenitis. However, the patient represented by sudden increase in the size of this mass 3 months ago associated with malaise and low grade fever but there was neither night sweat nor weight loss. The patient had a clear evidence of contact with cats because he was a veterinarian. There was no other positive family, surgical or medical history.

The previous histopathology report was the typical of toxoplasmic lymphadenopathy, it said that the 1.5 cm level IV lymph node showed "obliteration of the normal architecture with preservation of sinuses, patchy follicular hyperplasia and increased vascularity. There was large numbers of histiocytes evident in the sinuses with granulomata scattered in various areas of the micro biopsy"

On examination, large, firm, mobile right sided lymphadenopathy mobile without signs of active inflammation in the overlying skin (level III, IV and V). No evident lymph nodes on the other side of the neck or other sites of his body and no hepatosplenomegaly. Temperature and vital signs were normal. ENT examination did not warrant any additional abnormality.

Laboratory Studies

Patient was sent to laboratory to assess his toxoplasmosis. Serological tests revealed border line titer of anti-toxoplasma IgM, positive anti-toxoplasma IgG, negative anti-toxoplasma IgA and high IgG avidity; these results indicated past infection of Toxoplasma gondii.

Erythrocyte Sedimentation Rate (ESR) was 95 mm/h. However, in men below the age of 50 it must be under 15 mm/hr. and the LDH level was 300 U/l these were the first red flag signs that directed the team to further evaluations for Lymphoma.

Full blood count, blood cell differential, blood film, renal function, liver function and electrolytes were all within normal limits.

Imaging studies

CT scan of the neck, from skull base to carina, revealed bilaterally enlarged lymph nodes with homogeneous enhancement; level II, III and IV in the right side and level IV and V on the left. However, neither mediastinal nor axillary L.Ns were detected.

Biopsy

Open surgical biopsy was done and 3 lymph nodes from the right level III and IV were taken and sent to the histopathology department for microscopic and Cytogenetic analysis which finally diagnosed it as grade III follicular non-Hodgkin's Lymphoma through the following:

Light microscopy revealed neoplastic follicles round to oval structure comprised of follicular center B-cells distributed evenly throughout the follicle, loss of normal lymphoid follicle contrast and loss of normal nodal architecture. Neoplastic follicles consist of a mixture of centrocytes and centroblasts; grade III follicular NHL (>15 large centroblasts /high-power field) was the diagnosis by light microscopy

DNA analysis showed t (14; 18) chromosomal translocation and fusion of the bcl-2 gene at 18q21 with the immunoglobulin heavy chain locus at 14q32.

Treatment

Patient was sent to the oncology department of the same institute to be fully evaluated and to start the suitable protocol for his cancer status. Staging identified no evidence of disease outside the neck. Combined chemotherapy followed by consolidation radiotherapy to the neck produced complete resolution of lymphadenopathy. The patient has remained well with no evidence of recurrence for 2 years.

Discussion

Toxoplasmosis is caused by *Toxoplasma gondii*, an obligate intracellular parasite. In healthy patients toxoplasmosis is often asymptomatic or may cause a mild febrile illness with the cervical lymph nodes, which may be clinically indistinguishable from other reasons of cervical lymphadenopathy [6]. However, in immunocompromised patients such as Lymphoma patient, like this case especially during chemotherapy, it may cause fatal illness like cerebral toxoplasmosis. So that special consideration must be given to association between toxoplasma and lymphoma [7].

Toxoplasmosis diagnosis is not an easy task because the ideal test has not been established. Antibody response often peaks before clinical symptoms; IgM antibodies appear within the first week of infection, peaks rapidly and then drop to low levels within weeks or months, IgG titers peak within 1-2 months and remain high but may fluctuate with time [8].

The avidity (functional affinity) of IgG antibodies have become standard to discriminate between recently acquired infection and those

obtained in the more distant past [9] Presence of high avidity antibodies essentially rules out infection acquired in the recent 3-4 months; by contrast, low avidity antibodies can persist beyond 3 months of infection[10]. The latex agglutination test is easy to perform and is sensitive but is less specific with a false positive rate of 1-2% [11]. Detection of *T. gondii* in tissue sections is occasionally possible using Wright or Giemsa stain [9] Histopathological changes in toxoplasmic lymphadenitis in immunocompetent individuals are frequently distinctive and diagnostic[12]

In healthy individuals the symptoms resolve spontaneously over several months and active treatment is rarely indicated. [13]. But Infections acquired by laboratory accident or transfusion of blood products are potentially most severe and should always be treated. Treatment is typically a combination of pyrimethamine, sulfadiazine and folinic acid for 4-6 weeks [14].

The non-Hodgkin's lymphomas are a group of neoplasms with histological, immunological and cytogenetic heterogeneity ranging from indolent tumours, such as follicular lymphoma and small lymphocytic lymphoma, which may spontaneously regress to highly aggressive with high mortality rate like precursor T- or B-lymphoblastic leukemia/lymphoma [15]. So that the NHL may present in mild symptoms and signs that do not stimulate the suspicious, like this case, but others may seek medical advice for severe symptoms and signs. Along with above mentioned variations, NHL's lymphadenopathy remits and relapses over several years, adding more ambiguity to the clinical picture.

Because histological diagnosis (light microscopy) cannot finally differentiate early stages of the indolent lymphomas, like follicular ones and the reciprocal t (14; 18) (q32; q21) constitutes the most common chromosomal translocation in human malignant lymphoid malignancies (it is present in 80-90% of NHL) [16], cytogenetic analysis rather than histology is the best methods to reach the final diagnosis and to avoid misinterpretations.

Association between Toxoplasmic lymphadenitis and lymphoma is not common in literature, recorded cases are very rare. As the natural history of NHLs is poorly understood, it is unknown if the toxoplasmosis infection was of any significance in the development of the lymphoma [17], another relation between both is clear in the opportunistic toxoplasma infection that happens in immunocompromised lymphoma patient in their end stages [18].

Conclusion

This case study emphasizes the importance of Cytogenetic analysis in histopathological examination of any persistent lymphadenopathy particularly the chronic cervical lymphadenopathy, which is very broad and confusing, to avoid missing serious cases like Lymphomas. Moreover, relation between toxoplasmosis, which infect one third of world's population and lymphoma must be extensively investigated.

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Conflicts of Interest

No conflicts of interest.

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