Author's response to reviews

Title: Small lymphocytic lymphoma with florid perniosis-like features: a case report

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Author's response to reviews: see over
Reviewer’s report

Title: Small lymphocytic lymphoma with florid perniosis-like features: a case Report

Authors:

Taylor M Morris
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Version: 2 Date: 26 April 2015

Author’s response to reviewers: see over
Reviewer's report

Title: Small lymphocytic lymphoma with florid perniosis-like features: a case Report

Version: 2 Date: 26 April 2015

Reviewer: Kedar Inamdar

Reviewer's report:

Major Revisions:
The authors describe an unusual cutaneous presentation of a low-grade CD5+ B-cell non-Hodgkin lymphoma (NHL) in a patient with previously diagnosed small lymphocytic lymphoma. The authors do a good and systematic review of dermatologic conditions associated with CLL/SLL, the differential diagnoses of primary versus secondary cutaneous B-cell NHLs and the incidence of histologic progression of CLL/SLL to large B-cell lymphoma (Richter transformation). The authors should clarify the following issues with regards to the diagnosis –

1. Authors should elaborate on the work-up of original diagnosis which led to the conclusion that this was indeed SLL. To that effect, provide information on which diagnostic modalities were used to establish the diagnosis. Was flow cytometry performed? Was cytogenetics done? The International Workgroup on CLL definition of SLL requires a. Lymphadenopathy b. no cytopenias due to bone marrow infiltration and c. <5000/uL peripheral blood B-cells. In the course of this patient's disease, there is no mention of patient having developed any lymphadenopathy. So how did the original diagnosis meet criteria for SLL?

- Immunophenotyping by flow cytometry performed on the bone marrow in 2004 confirmed a lambda monoclonal B-cell proliferation with CD5 and CD19 co-expression. CD20 expression was evident but no evidence of CD23 or CD10 staining. FMC7 was negative.

- Cytogenetics, other than FISH for cyclin D, was never performed.

- On review of the patient's chart, he was not noted to have lymphadenopathy or splenomegaly when he initially presented to our cancer centre in 2004. Ultrasounds of the abdomen did not detect significant lymphadenopathy or splenomegaly. However, in my first encounter with the patient in April 2013, I noted palpable lymph nodes in the left anterior cervical chain, the axillae and the left groin. The largest lymph node was estimated to be 1 centimeter. This information has been included in the revised manuscript. There has never been any documented cytopenia due to bone marrow infiltration.
• The peripheral blood at first presentation in 2004 showed a WBC of 6.9 x 10^9/L (4.0-10.5), neutrophils 4.43 x 10^9/L (2.00-7.00), lymphocytes 1.89 x 10^9/L (1.5-4.00) hemoglobin 145 g/L (136-170), and platelets 307 x 10^9/L (150-400). The peripheral blood smear showed normal red blood cell morphology. The platelets were adequate in number and normal in morphology. Neutrophils were also normal in number and unremarkable in morphology. Lymphocytes were normal in number with scattered reactive forms but no smudge cells. The remainder of the leukocyte differential was unremarkable. Repeated peripheral blood counts over the last 10 years have never shown a lymphocytosis. This information has been included in the revised manuscript.

2. While cyclin D1 is negative and excludes a classic mantle cell lymphoma, how was the possibility of cyclin D1 negative mantle cell lymphoma ruled out. This is particularly important to exclude considering the unusual presentation of SLL in this patient and the lack of CD23 expression by the neoplastic lymphoid cells.

• We believe that the lack of CD23 expression was due to an unusual presentation of SLL. Although CD23 is usually positive in CLL/SLL, CD23 negative CLL/SLL is not rare. The negative FMC7, and cyclin D expression, together with negative FISH for the t(11;14), argue against mantle cell lymphoma. CD23 expression may be dim in a minority of CLL/SLL cases, making interpretation more difficult. However, the use of other immunological markers as mentioned above can help to differentiate CLL/SLL from other lymphoid malignancies. We have included this information in the revised manuscript, including a reference (Zhao XF. Pitfalls in diagnostic hematopahtology: Part I. Int J Clin Exp Pathology. 2009 2: 11-20). Mantle cell lymphomas usually follow a more aggressive course while our patient has had a very indolent course, only requiring treatment because of cutaneous infiltration.

3. Lymphomas other than CLL/SLL or mantle cell lymphoma can aberrantly express CD5 particularly marginal zone lymphoma, lymphoplasmacytic lymphoma, follicular lymphoma. While follicular lymphoma is excluded, how were other entities excluded from differential diagnosis?

• Although CD23 expression is usually seen in CLL/SLL, CD23 negative cases are not rare [2]. The negative FMC7 and cyclin D1 expression and absent t(11;14) virtually excludes the diagnosis of mantle cell lymphoma. Furthermore, mantle cell lymphoma usually follows a more aggressive course while our patient had a very indolent course, only requiring treatment because of his painful fingers. Lymphoplasmacytic lymphoma (LPL) can rarely be CD5-positive. However, our case did not show plasmacytoid cytologic features, was FMC7-negative, the surface Ig
expression was dimmer than would be expected in LPL, and an IgM paraprotein was never detected. The appearance of the monoclonal lymphoid infiltrates seen in the biopsies without the typical clear abundant cytoplasm often observed in marginal zone lymphoma, together with the positive CD5 expression and negative FMC7 seen in this case make a diagnosis of marginal zone lymphoma less likely as well. However, CD5-positive marginal zone lymphomas have been reported. We have added this information to the manuscript.

Minor essential revisions -
None

Discretionary revisions –

It would be helpful to add a figure of CD3 and CD23 immunostains if available.

• The CD3 and CD23 were negative on all tissue biopsies and bone marrow. A photomicrograph of the negative stains can be added if required.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.
Reviewer's report

Title: Small lymphocytic lymphoma with florid perniosis-like features: a case Report

Version: 2 Date: 1 May 2015

Reviewer: Mingyi Chen

Reviewer's report:
1. The conventional immunophenotype of CLL/SLL is CD5+/CD20 dim+/CD23+/FMC-/Cyclin D1-. The author should discuss why CD23 is negative in this case.

   • Although CD23 is usually positive in CLL/SLL, CD23 negative CLL/SLL is not rare. The negative FMC7 and cyclin D expression, together with negative FISH for the t(11;14), argue against mantle cell lymphoma. CD23 expression may be dim in a minority of CLL/SLL cases, making interpretation more difficult. However, the use of other immunological markers as mentioned above can help to differentiate CLL/SLL from other lymphoid malignancies. We have included this information in the revised manuscript, including a reference (Zhao XF. Pitfalls in diagnostic hematopathology: Part I. Int J Clin Exp Pathology. 2009 2: 11-20).

2. I would like to see a peripheral blood smear and possible flow cytometry data on this case.

   • The peripheral blood at first presentation in 2004 showed a WBC of 6.9 x 10^9/L (4-10.5), Neutrophils 4.43 x 10^9/L (2.00-7.00), Lymphocytes 1.89 x 10^9/L (1.5-4.00) Hemoglobin 145 g/L (136-170), and platelets 307 x 10^9/L (150-400). The peripheral blood smear showed normal red blood cell morphology. The platelets were adequate in number and normal in morphology. Neutrophils were also normal in number and unremarkable in morphology. Lymphocytes were normal in number with scattered reactive forms but no smudge cells. The remainder of the leukocyte differential was unremarkable. Repeated peripheral blood counts over the last 10 years have never shown a lymphocytosis.

   • Immunophenotyping by flow cytometry performed on the bone marrow in 2004 confirmed a lambda monoclonal B-cell proliferation with CD5 and CD19 co-expression. CD20 expression was evident but no evidence of CD23 or CD10 staining.
3. The author should also mention if the patient has lymphadenopathy or splenomegaly.

- On review of the patient’s chart, he was not noted to have lymphadenopathy or splenomegaly when he initially presented to our cancer centre in 2004. Ultrasounds of the abdomen did not detect significant lymphadenopathy or splenomegaly. However, in my first encounter with the patient in April 2013, I noted palpable lymph nodes in the left anterior cervical chain, the axillae and the left groin. The largest lymph node was estimated to be 1 centimeter. This information has been included in the revised manuscript.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
No
Reviewer's report

**Title:** Small lymphocytic lymphoma with florid perniosis-like features: a case report

**Version:** 2 **Date:** 6 May 2015

**Reviewer:** Wayne Tam

**Reviewer's report:**
In this case report, Morris described a case of small lymphocytic lymphoma presenting with florid perniosis-like features during the course of disease. Although various cutaneous presentations of CLL/SLL have been reported, this type of cutaneous presentation is very unusual and to my understanding, has not been reported.

**Major Compulsory Revisions**

1. The peripheral blood count (CBC) needs to be stated in detail.
   - The peripheral blood at first presentation in 2004 showed a WBC of 6.9 x 10^9/L (4-10.5), Neutrophils 4.43 x 10^9/L (2.00-7.00), Lymphocytes 1.89 x 10^9/L (1.5-4.00) Hemoglobin 145 g/L (136-170), and platelets 307 x 10^9/L (150-400). The peripheral blood smear showed normal red blood cell morphology. The platelets were adequate in number and normal in morphology. Neutrophils were also normal in number and unremarkable in morphology. Lymphocytes were normal in number with scattered reactive forms but no smudge cells. The remainder of the leukocyte differential was unremarkable. Repeated peripheral blood counts over the last 10 years have never shown a lymphocytosis.

2. The bone marrow, liver and gall bladder pathology is vague and needs to be described in greater detail. The immunophenotype of the neoplastic B cells in these sites has to be stated. The differential diagnosis of a CD5-positive marginal zone lymphoma cannot be excluded, and the diagnosis of an SLL cannot be definitively concluded with the current data.
   - The biopsy of the left upper ear showed a dense infiltration of subcutaneous tissue by a small lymphocytic infiltration distributed in a diffuse pattern. The majority of cells showed a slightly irregular nuclear contours, condensed chromatin and small amounts of cytoplasm. Only rare mitotic figures are identified. Occasional loose collections of prolymphocytes suggestive of growth centres were seen. There was no evidence of prolymphocytic or large cell transformation. CD 5, CD 10 and CD 20, CD45 were positive, while CD 3 and CD 23 were negative.
• The bone marrow showed a subtle interstitial lymphoid infiltration of small cells with mature chromatin constituting less than 20% of the marrow. Immunophenotyping by flow cytometry performed on the bone marrow confirmed a lambda monoclonal B-cell proliferation with CD5 and CD19 co-expression. CD20 expression was evident but no evidence of CD23 or CD10 staining. FMC7 staining was negative. This information will be included in the revised manuscript. Despite the finding of the absence of CD23 expression, the findings, including the occasional growth centres, are most consistent with small lymphocytic lymphoma.

• We have added more information on the gallbladder and the liver pathology to the manuscript. In addition to cholelithiasis, there was a background population of B-lymphocytes co-expressing CD5 and CD20 with no evidence of CD23, CD 10 or Cylcin-D1 expression. A liver biopsy performed the same year to investigate abnormal liver function tests showed marked lymphocytic and plasmacytic infiltration as well as reactive secondary follicles predominately involving the portal tracts, suggestive of autoimmune hepatitis but with an unusual degree of lymphocyte infiltration with the same phenotypic profile as the gallbladder.

3. The discussion was not well written and appeared too focused on cutaneous malignancies associated with CLL. It should be more devoted to discussing specific cutaneous manifestations caused by leukemic cutis, followed by other cutaneous manifestations closely associated with CLL/SLL, but without lymphoid infiltrate, and finally neoplastic and non-neoplastic dermatologic conditions associated with CLL/SLL.

• The discussion has revised as per the suggestions of the reviewer.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.