Double IgA Bands in Serum from a Patient with Lymphoplasmacytoid Leukemia with Hairy-Cell Morphology

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We present a case of plasmacytoid lymphocytic leukemia with hairy-cell-like cytoplasmic projections and separate monomeric and polymeric IgA(\(\lambda\)) serum bands confirmed by immunofixation. After a prolonged initial good response to chemotherapy, the patient had recurrent disease with increased plasmacytoid blastic feature and died. The relationship of this case to B-cell proliferative disorders is discussed.

Additional Keyphrases: cancer · chemotherapy · B cells · immunoglobulins · immunofixation

Lymphoplasmacytoid, plasma cell, and B-cell neoplasms may have overlapping immunological and clinical features. We present one such case.

Case History

A 55-year-old man presented with fever and weight loss. At presentation, his leukocyte count in peripheral blood was 35.3 \(\times\) 10\(^9\)/L, of which 42% were small mostly lymphoplasmacytoid lymphocytes with long filamentous hairy-cell-like cytoplasmic projections (Figure 1). The hairy-cell-like morphology was seen repeatedly on blood smears freshly prepared during his hospital course. Bone marrow from the iliac crest had 98% cellularity, 90% of the cells being plasmacytoid lymphocytes with hairy-cell-like morphology (Figure 1). A few Russell bodies, Dutcher body intranuclear inclusions, and atypical plasma cells were also present. A diffuse, closely packed infiltrate was seen in the needle biopsy, in contrast to the widely spaced honeycomb pattern typical of hairy-cell leukemia, and the tumor cells exhibited tartrate-sensitive acid phosphatase (EC 3.1.3.2) activity. Immunoperoxidase studies revealed that 90% of the lymphoid cells had lambda light chains, only 3% of the cells having kappa light chains.

Electrophoresis of serum proteins revealed two distinct separate bands in the beta-gamma region, and there was an above-normal value for IgA, 10.9 g/L (reference range for normal 0.70–3.12 g/L). Immunofixation electrophoresis revealed one narrow and one separate broad band, both with IgA (\(\lambda\)) immunoreactivity. After pre-reduction with 2-mercaptoethanol, a single IgA (\(\lambda\)) band remained (Figure 2), which suggested that monomeric and polymeric IgA(\(\lambda\)) bands had been present. Dysproteinemia was manifest as follows: decreased IgG, 2.83 g/L (normal 6.39–13.49 g/L); and decreased IgM, 0.355 g/L (0.56–3.52 g/L). In the patient's urine, a 257 mg/24 h monoclonal band found on electrophoresis was identified as free lambda light chains on immunoelectrophoresis and immunofixation. There were no clinical features of Waldenström's macroglobulinemia. Mild hepatomegaly and mild increases in results of liver-function tests were noted initially, but no hepatomegaly was noted on subsequent physical examinations. No lymphadenopathy or splenomegaly was found on repeated examinations, and results of an initial abdominal computed tomography were unremarkable.

The patient's leukemia was initially treated with one cycle of vincristine and cyclophosphamide and he was continued on prednisone. His pulmonary infiltrates resolved. Shortly after presentation, he developed thrombocytopenia, with the platelet count going as low as 13.0 \(\times\) 10\(^9\)/L, unresponsive to prednisone and immunosuppressive therapy, including cytarabine, vincristine, and azathioprine.

Decreased platelet survival after platelet transfusions was demonstrated, and the patient underwent splenectomy. The removed spleen was of normal size (323 g), with only focal mild reactive changes of the white pulp. Post-splenectomy platelet counts slowly increased, and he was continued on prednisone, with his platelet count returning to normal (299.0 \(\times\) 10\(^9\)/L) with therapy his initial leukocytosis of 35.3 \(\times\) 10\(^9\)/L resolved. However, repeated examination of his bone marrow revealed persistent small foci of lymphoplasmacytoid infiltrates. An associated marked decrease in his monoclonal gammopathy was also noted. Serum protein electrophoretic pattern and immunoglobulin concentrations were within normal limits 10 months after initial presentation. However, at 12 months he had onset of fatigue and weight loss with reappearance of the IgA monoclonal gammopathy.

The peripheral blood leukocyte count at relapse was 16.2 \(\times\) 10\(^9\)/L with 58% neutrophils, 5% bands, 1% metamyelocytes, 6% eosinophils, 10% monocytes, and 20% lymphocytes with a low population of plasmacytoid lymphocytes. Examination of the bone marrow at this time revealed 80% cellularity, the presence of multiple lymphoid nodular aggregations, and a diffuse increase in atypical plasmacytoid lymphocytes. A spectrum of immature plasmacytoid cells were seen, including multinucleated and lobated larger cells with nucleioli, and smaller atypical plasma cells with prominent juxtanuclear hof (Figure 3). Several of these cells revealed frayed cytoplasmic borders with cytoplasmic projections, but not the prominent hairy-cell-like pattern seen on the previous bone-marrow examinations. The cells exhibited IgA(\(\lambda\)) immunoreactivity, and studies of his serum immunoglobulins revealed a return of the dysgammaglobulinemia, with an IgA value of 0.12 g/L. A radiographic skeletal survey showed no lytic bone lesions and no lymphadenopathy or hepatomegaly. He developed persistent thrombocytopenia and fever despite intensive therapy with pulsed alkylator agents with prednisone 50 mg twice daily and melphalan 12 mg daily for four days, each of these orally, and vincristine, 1 mg intravenously, every two weeks; prednisone, 10 mg orally, was given between the four-day cycles. Three months later, his chemotherapy was changed to cyclophosphamide, 500 mg weekly, and prednisone 50 mg every other day. Adriamycin (13 mg) and vincristine (0.5 mg) by 24-h infusion and dexamethasone, 40 mg daily intravenously for four days were also used, without improvement in his condition. No infectious etiology for his fever was found.

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His general condition deteriorated. He desired no further therapy and died 18 months after his initial presentation. Permission for autopsy examination was refused.

**Discussion**

This case has several unusual features. The presence of prominent hairy-cell-like cytoplasmic projections, both in the peripheral blood and bone marrow, initially warranted consideration of hairy-cell leukemia in the differential diagnosis. The absence of tartrate-resistant acid phosphatase cytoplasmic activity or splenic involvement, and the characteristic loosely packed arrangement of cells with a halo-like appearance on bone marrow biopsy, clearly established that this case was not hairy-cell leukemia. It is now well documented that other cases of malignant lymphoma and leukemia may have circulating atypical lymphoid cells with "hairy" cytoplasm (1). In the study by Neiman et al. (2), six of the 10 patients with well-differentiated lymphocytic lymphoma with circulating lymphocytes with hairy cytoplasm had plasmacytoid differentiation; one patient had an absolute lymphocytosis, similar to our case. Although hairy-cell morphology may also result as an artifact of improper blood film preparation (3), or with prolonged exposure of blood to anticoagulant (4), cold storage, or Ficoll–Hypaque sediment gradient (5), no such factors were identified in this case, the hairy-cell-like morphology being seen repeated in freshly prepared blood smears. The lineage of hairy-cell leukemia has been controversial. In a recent immunological typing study, Anderson et al. (6) suggested that hairy-cell leukemia may be a tumor of pre-secretory B-cells (pre-plasma cells). Cases of hairy-cell leukemia with associated macroglobulinemia (monoclonal IgM production) (7), and of hairy-cell leukemia and associated myelomatosis (8), have also suggested the possibility of closely related disorders of divergent differentiation from a common B-cell precursor (8). Cases clinically fitting Waldenström's macroglobulinemia...
have been associated with production of IgM as well as IgG and IgA monoclonal proteins in serum, the presence of polymeric immunoglobulins (in particular IgM paraproteinemia) predisposing to serum hyperviscosity and clinical macroglobulinemia. Macroglobulinemia, although classically associated with lymphoplasmacytoid neoplasias, has been seen with small lymphocytic lymphoma, chronic lymphocytic leukemia, other B-cell lymphomas, rare cases of plasma cell myeloma, and other leukemias; it has also been unassociated with morphological lesions or with only benign lymphoid aggregates seen in the bone marrow (9). Occasional cases of lymphoplasmacytic tumors exhibiting multiple immunoglobulin production have been documented. One case of lymphoplasmacytic lymphoma initially associated with IgM(kappa) monoclonal protein evolved to produce three separate monoclonal proteins: IgG-kappa, IgA-kappa, and IgM-kappa (10).

Serum from the present patient showed two electrophoretic bands corresponding to monomeric and polymeric IgA (lambda) bands. The polymeric band, which is wider, is probably related to the formation of dimers and polymers of variable size. This is analogous to the more broadly based single bands seen with IgA plasma cell myeloma, which can also be associated with two bands of monomers and polymers, similar to this case (11). The presence of polymers, molecular asymmetry, the interaction of IgA with other proteins, as in the formation of IgA-albumin complexes, may all have a role in the production of hyperviscosity (12).

Whereas the course of plasmacytoid lymphocytic lymphoma and Waldenström macroglobulinemia cases has been variable, some cases have been complicated by the development of immunoblastic large cell lymphoma (13). Moreover, chronic lymphocytic leukemia cases may also evolve into an acute phase, including development of diffuse immunoblastic lymphoma (Richter's syndrome), prolymphocytic transformation, acute blastic crises, and (rarely) multiple myeloma (14). In our case, although the development of refractory disease was associated with increasing pleomorphism and immature plasmacytic morphologic features, no overt picture of large cell immunoblastic lymphoma or multiple myeloma had been noted, although we have no results of autopsy examination.

In summary, this case of lymphoplasmacytoid leukemia presented three interesting or uncommon features: (a) the production of monomeric and polymeric IgA(lambda) separate bands, (b) hairy-cell-like morphology, and (c) progression into refractory disease with increased plasmacytoid and pleomorphic features.

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References