case report

Large B-cell transformation of chronic lymphocytic leukemia presenting as a penile mass and skin lesion

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A 77-year old man was referred to our department in January 2007 after developing a painful penile mass 2 months before. He had a history of chronic lymphocytic leukemia (CLL) for ten years. Two years before his referral he had received 12 courses of chlorambucil and prednisolone for the control of resistant autoimmune hemolytic anemia.

On physical examination there was splenomegaly (4 cm below the left costal margin) without palpable lymphadenopathy. Two violaceous nodular skin lesions with maximal diameters of 3 and 4 cm were evident in the left (Figure 1) and right forearm, respectively, as well as enlargement and hard infiltration of the base of the penis. Laboratory work-up revealed a positive direct anti-globulin Coombs test (IgG) and the presence in the serum of IgGk monoclonal immunoglobulin. He had no anemia, thrombocytopenia or blood lymphocytosis. A CT scan of the thorax and abdomen revealed a normal lung parenchyma and mediastinum, an absence of enlarged lymph nodes and only moderate splenomegaly. The patient underwent sonographic examination of the penis. A large ill-defined, heterogeneous, hypoechoic mass was shown infiltrating the corpora cavernosa. Color Doppler examination showed rich tumor vascularity. A pelvic MRI, using T2-weighted unenhanced and contrast-enhanced T1-weighted images confirmed the presence of a mass infiltrating the corpora cavernosa and extending around the penile shaft with heterogeneous enhancement after contrast material administration (Figure 2). The mass invaded the corpus spongiusum, not extending to the urethra. Ultrasound-guided penile biopsy and bilateral skin lesion biopsies were performed. Histopathologic examination revealed a diffuse infiltration by large B-lympocytes (centroblast and immunoblast) (Figure 3). Tumor cells were CD45, CD20 and bcl-6 positive and CD5, CD10, CD23, cyclin D3 and MUM1 negative. A diagnosis of diffuse large B-cell lymphoma was established. Bone marrow biopsy showed diffuse infiltration by small B-lymphocytes CD20, CD20, CD23 positive and CD10 and bcl-6 negative. Confluent sheets of large cells were not found and a diagnosis of CLL was made.

Administration of the anti-CD20 monoclonal antibody rituximab (Mabthera, Roche) at 375 mg/m^2 in combination with standard dose CHOP chemotherapy resulted in complete resolution of penile pain within 2 weeks and significant improvement of the penile enlargement. The patient is currently asymptomatic, in clinical complete remission and continues therapy.

The transition from an indolent leukemia as CLL to an aggressive large B-cell lymphoma is described as Richter syndrome. It can occur at any time during

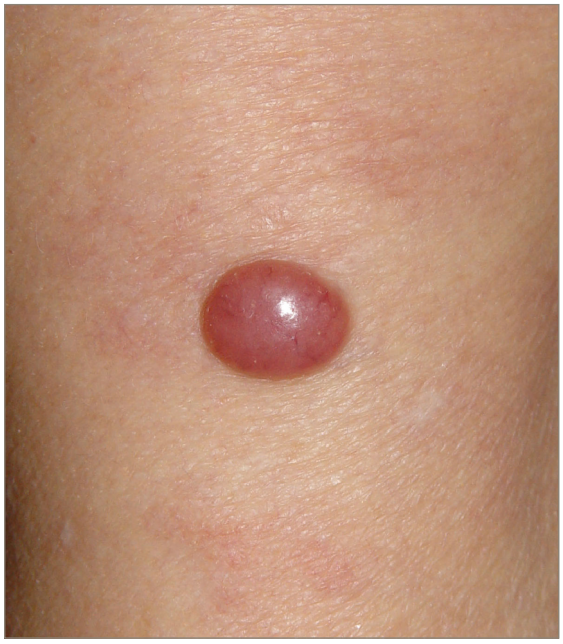

Figure 1. Skin lesion on the left forearm.

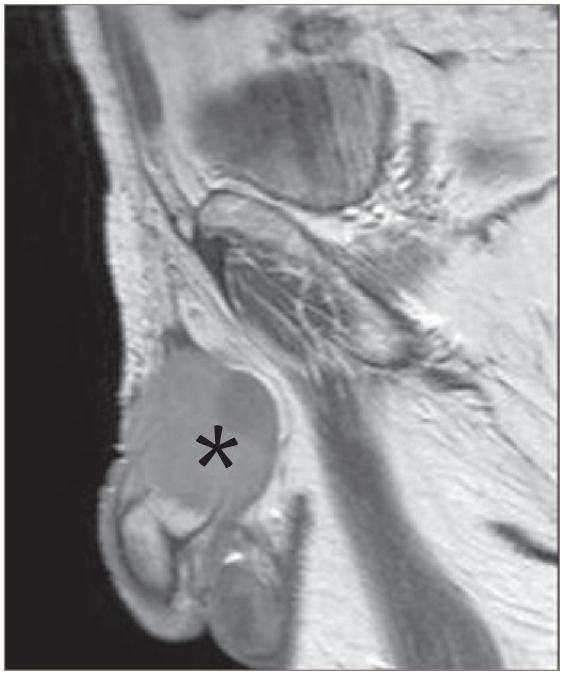

Figure 2. MRI of the penis. Post-contrast T1 weighted image demonstrates a mass (asterisk) invading the corpora cavernosa. The tumor is seen extending to the corpus spongiusum, without invading the urethra.

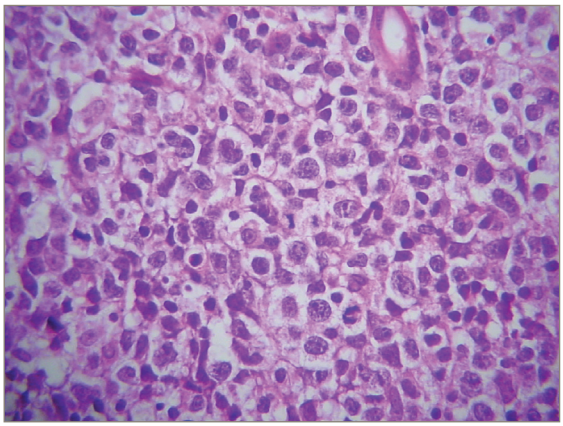

Figure 3. Large B-cell transformation of chronic lymphocytic leukemia in the penis (hematoxylin and eosin ×400).

the course of the disease, with an incidence of approximately 3.5% for patients with CLL.[1] Richter syndrome is characterized by increasing lymphadenopapthy, splenomegaly, fever and weight loss. Patients also may have extranodal involvement with infiltration of the kidneys, lungs, gastrointestinal tract and central nervous system.[2] Ours is the only report of CLL transformation to a high-grade B-cell lymphoma affecting the penis and skin, both relatively uncommon sites for this entity. In Richter's syndrome the marrow is infiltrated only in a minority of cases. In the majority of patients, as in our case, the marrow shows the characteristic features of CLL.[3]

Although the large cell lymphoma observed in our case could represent an independent B-cell malignancy, it is more likely that it is secondary to clonal transformation of the original CLL disease.[4] Trisomy 12, deletions of chromosome 11 and other genetic defects are more often described in patients with Richter syndrome than in patients with CLL.[5] The existence of these karyotypic abnormalities can cause proliferation, acquisition of additional cytogenetic aberrations and transformation to aggressive lymphoma. In addition, in these immunocompromised patients, clonal evolution may be triggered by viral infections.[5] Characterization of immunoglobulin heavy-chain gene rearrangements expressed by the original leukemic cells and large cell lymphoma clone of patients with Richter transformation can demonstrate that such lymphomas arise from the original CLL clone.

We managed our patient with chemoimmunotherapy in view of the CLL background, the multi-site involvement by lymphoma and the positive impact of rituximab on the outcome of patients with B-cell lymphomas. He received the combination rituximab-CHOP, a therapy that has shown to overcome bcl-2 mediated resistance and prolong survival in elderly patients with DLBCL. Despite the rapid response of the disease the prognosis seems to be poor with median survival ranging from 5 to 8 months.[5]

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