Chest Wall Swelling, A Rare Presentation of Richter's Transformation

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Received: 4 May 2010 / Accepted: 26 July 2010 / Published online: 1 October 2010
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Abstract A large cell lymphoma develops in approximately 1–10% of chronic lymphocytic leukemia (CLL). This is known as Richter's syndrome. Chest wall swelling is a very unusual presentation of this syndrome. Here we report another such case of chest wall swelling, a very rare presentation of Richter's syndrome.

Keywords Chronic lymphocytic leukemia · Chest wall swelling · Large cell transformation · Richter's transformation

Case Summary

51 years old female was diagnosed to have CLL, RAI stage III in October 2003 when she presented with symptomatic anemia. Patient had undergone splenectomy in the past for hypersplenism cause of which was not ascertained. Patient was on follow up for about a month as patient had no active complaints with unremarkable examination except splenectomy scar and her CBC revealed stable counts varying from 30,000 to 40,000 white blood cells/mm³. LDH was 668 mg/dl with rest of serum chemistry within normal limits. Other detail investigations could not be carried out due to financial constraints. Patient was put on chlorambucil 10 mg daily on 28th November 2003 when CBC revealed Hb 9.2, TLC 173.6, DLC P10, L89, E1, platelets 101. Counts down sloped and were normalized in January 2004 (TLC 6.3). Due to non availability of chlorambucil in April 2004 patient

was shifted to cyclophosphamide 50 mg bid and prednisolone 40 mg daily till February 2005 when chlorambucil was restarted and cyclophosphamide stopped. The CBC done on 18th February 2005 showed a rise in TLC to 13.3 and 14.94 on 25th March 2005. This was attributed to some missed doses by the patient because of financial constraints, so patient was again started on tab. Cyclophosphamide in June 2005. Patient was continued on tab. Cyclophosphamide and prednisolone was stopped in January 2006 as the patient got puffiness of face. Patient was in clinical remission till July 2009 when she presented with a swelling in left clavicular area which developed in 2 months period. On examination there was almost a bony hard swelling measuring 4 × 4 cms, fixed and occupying 2/3rd space in left parasternal area. CBC that time revealed Hb 10.4, TLC 7.35, DLC P56, L25, M14 and platelets 123. Chest X-ray unremarkable.

FNAC of the swelling Showed lymphoid cells mixed (small and large) compatible with leukemic deposits i.e. CLL with large cell transformation (Recheiter's disease).

In view of development of Recheiter's disease cyclophosphamide was stopped and was advised cyclophosphamide, vincristine and prednisolone (CVP) combination. Patient received first cycle of CVP on 07.09.2009. On follow-up as on 18.09.2009 swelling was not appreciable and patient's CBC revealed Hb. 7.2 g, TLC 5.20, DLC P65, L32, E2, M1 and platelet 100. Patient received 6th cycle of CVP on first December 2009. Currently patient is on follow up with normal physical and normal CBC. (Figs. 1, 2).

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Discussion

Richter's transformation (RT, Richter syndrome) was first described in 1928 by Maurice Richter as the development

Fig. 1 Chest wall swelling in the left parasternal area

Fig. 2 FNAC of swelling showing mixed lymphoid cells (small and large)

of an aggressive large-cell lymphoma in the setting of underlying chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The incidence of RT from CLL/SLL has been variously estimated at 2–9%, [1–3] making it less common than histologic transformation of other low-grade mature B cell malignancies. Recent studies have suggested that the development of RS may be related to the evolution of an abnormal clone unrelated to the underlying CLL clone. Clearly identifiable risk factors for the development of RS are lacking, and its development has been shown to be independent of the disease stage, duration of the disease, type of therapy or response to therapy. The median time from the diagnosis of CLL/SLL to transformation has been in the range of two to four years [2, 4, 5]. However, the presence of diffuse lymphomatous involvement, advanced Rai stage, ZAP-70 expression, high LDH and β 2M levels may predict the development of RS. Laboratory abnormalities include anemia, neutropenia, and thrombocytopenia due to large cell transformation in the bone marrow. A rapid increase in the serum LDH is seen in the majority of patients, with a significant proportion of

patients also exhibiting paraproteinemia. The diagnosis is generally made on examining the histology of a rapidly enlarging lymph node, which typically reveals large cell lymphoma. Even though a significant proportion of patients with advanced CLL and RS have abnormal cytogenetics, their prognostic significance has not been established. Trisomy of chromosome 12 in the presence of a complex karyotype may have some correlation with aggressive disease although it is unlikely to be the only cytogenetic abnormality contributing to the lymphomatous transformation.

Transformations of CLL to either prolymphocytic leukemia or large cell lymphoma (Richter transformation) is often associated with immunophenotypic drift, where CD5 is lost and FMC7 expression is acquired. Additionally, expression of CD20 and surface immunoglobulin typically becomes brighter in PLL or Richter transformation. Although the morphological appearance of prolymphocytes or large cells in blood, bone marrow or lymph nodes is typically adequate to make the diagnosis of transformation, flow cytometry may be useful in cases where morphological findings are less clear.

Recheiter's syndrome occurs most commonly in lymph nodes and may represent a second neoplasm or a transformation from the same clonal population. Recheiter's syndrome (RS) is characterized by rapid lymph node enlargement, splenomegaly, hepatomegaly, fever, weight loss and is associated with a rapid fatal outcome [4, 6, 7]. RS frequently arises in the lymph nodes or bone marrow and rarely presents with extra nodal involvement which includes the gastrointestinal tract, eye testis, central nervous system, lung, kidney and skin [8]. RS has also been noted to occur in nose, skin bone and bronchus [9]. Extra nodal sites include the gastrointestinal tract (5.1%), lung (2.5%), pleura (10.2%), oropharynx (7.7%), bone (2.5%), and marrow (5.1%) and also the central nervous system (12.8%). In rare cases, CNS symptoms may be the only initial manifestation of RS. Richter's transformation of CLL to diffuse large B-cell lymphoma, PET/CT has overall sensitivity, specificity, and positive and negative predictive values of 91, 80, and 53 and 97% respectively [9]. Richter transformation may be triggered by viral infections, such as Epstein-Barr virus, which are common in immunocompromised patients. Trisomy 12 and 11 abnormalities, as well as multiple genetic defects, have been described in patients with Richter's syndrome. Multiple genetic defects, such as mutations such as mutations of the p^{53} tumor suppressor gene, $p16INK4A$, and p^{21} , loss of p^{27} expression, deletion of retinoblastoma, increased copy number of C-MYC, and decreased expression of the A-MYB gene, have been described. These abnormalities may cause CLL cells to proliferate and by facilitating the acquisition of new genetic abnormalities to transform into RS [1].

There are no laboratory findings that are specific for RS. Anemia with hemoglobin less than 11 g/dl is seen in about 50% of cases and thrombocytopenia with a platelet count less than 100,000/ μ l in 43% [10] there may be elevation of LDH levels, which can be a marker for tumor growth. 82% of patients present with LDH levels twice as high as upper limit of normal, as opposed to CLL in which only 8% of cases demonstrate elevated LDH levels [4]. The clinical course of RT is rapidly progressive, with a median survival of 5–8 months [1, 4, 11, 12].

Treatment

Historically, RS has been treated with regimens similar to those used for the treatment of large-cell lymphomas involving multiple agents like methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin, dexamethasone, cytarabine, and cisplatin (e.g., MACOP-B, CHOP-B, DHAP, and VAD). The best overall response rates of approximately 40% have been recently reported and the CFA (cyclophosphamide, fludarabine, cytarabine) and hyper CVXD (fractionated cyclophosphamide, vincristine, liposomal daunorubicin, dexamethasone, and rituximab) regimens. The duration of response and the overall survival rates are dismal, with most patients likely to die within 6 months of their diagnosis despite aggressive therapy. Long-term remissions and survival have been reported in a few patients following allogeneic stem cell transplant but this approach is associated with an extremely high 30-day transplant mortality of around 38%.

Therapeutic strategies include intensive chemotherapy, monoclonal antibodies, and stem cell transplantation. The response rates range from 5 to 43%. (Complete response, 5–38%) and the median survival duration ranges from 5 to 8 months. Current treatments are aggressive, but prognosis is poor. Novel curative treatment strategies are needed.

Radiotherapy is used to treat brain or spinal cord and to control pain from enlarged lymph nodes.

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