Very Late Relapse of Hodgkin's Lymphoma

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Late relapses of Hodgkin's lymphoma (more than 5 years) following radiation therapy occur in 5–10% of patients, and are more commonly seen following combined modality therapy [1]. Bodis et al. [2] reported relapse occurring more than 5 years after radiation therapy for stage I-II Hodgkin's disease in 3.5% of 1,082 patients. Patients suffering from late and very late relapse may have the same long-term outcome as patients who do not relapse [3]. Relapses after more than 10 years are very rare. We present a young woman with a very late relapse of HL that occurred 17 years after diagnosis.

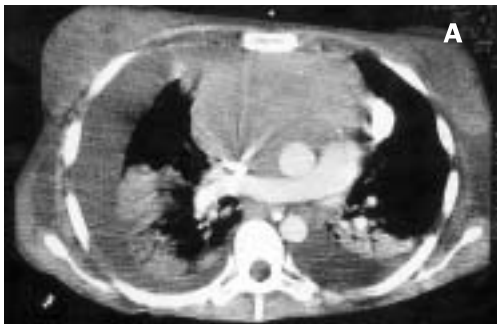
Patient Description

A 30 year old woman was admitted to our department because of chest pain and shortness of breath. Seventeen years previously, in Russia, a chest X-ray for chronic cough and fever demonstrated a mediastinal mass. A needle biopsy revealed Hodgkin's lymphoma of the nodular sclerosis type, stage II. She underwent radiotherapy and prolonged chemotherapy (12 courses of mechlorethamine, vincristin, procarbazine and prednisone – MOPP), was considered to be in complete remission, and did not receive consolidation therapy.

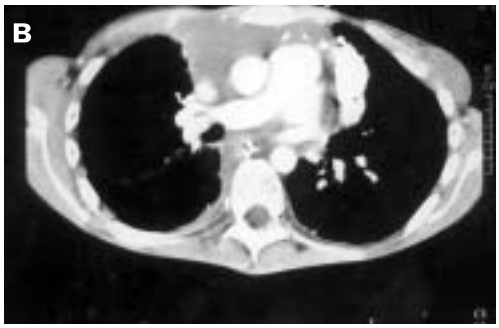
On admission she looked pale and dyspneic. Physical examination was normal except for a few rales in both lower lungs. A huge mediastinal mass constituting some 80% of the chest diameter was seen on chest X-ray. Mild hypercalcemia of 11.3 mg/dl (normal 8.5–10.5 mg/dl) was also found. Histopathology revealed a relapse of Hodgkin's lymphoma of the nodular sclerosis type. The diagnosis was confirmed by an expert hemopathologist; most malignant cells demonstrated positivity for CD 30.

At this stage the patient refused therapy, was discharged, and did not return for follow-up. One year later she was hospitalized again with acute respiratory failure requiring mechanical ventilation. Large bilateral pleural effusions, pressure of the mediastinal mass on the large bronchi, and a probable weakness of respiratory muscles due to severe catabolic state and malnutrition all contributed to the respiratory failure. Her arterial blood gases were compatible with respiratory acidosis due to ventilatory failure and severe hypoxemia (PaO_2 46 mmHg, PCO_2 101 mmHg, Bic 44.6 mEq, saturation 92%). Her condition stabilized with mechanical ventilation and broad-spectrum antibiotics. Computerized tomography of the chest and abdomen revealed a giant mediastinal mass, massive bilateral lung infiltration, large bilateral pleural effusions and ascites [Figure A].

Paracentesis of the ascites revealed an exudative fluid with 2,700 cells (77% of them neutrophils). *Streptoccocus hemolyticus* group G grew from ascitic fluid cultures. No obvious source for the peritonitis could be found (gynecologic examination and transvaginal ultrasound were normal). Within a week her physical condition improved, the fever resolved and mechanical ventilation was no longer required. At that stage, the patient agreed to chemotherapy. She was treated with eight monthly courses of the ABVD regimen (doxorubicin, bleomycin, vinblastin and dacarbazine), which led to a rapid and impressive shrinking of the mediastinal mass [Figure B]. Because of the still poor general condition of the patient, it was decided not to perform a Gallium or positron emission tomography scan in



[A] CT scan before treatment of huge mediastinal mass, bilateral infiltration and pleural effusion.



[B] CT scan post-treatment, showing disappearance of mediastinal mass and lung infiltration.

HL = Hodgkin's lymphoma

order to confirm complete remission. The treatment was stopped with the CT still showing minimal abnormalities.

One year after completion of therapy she is still in complete remission with no major side effects and a good quality of life.

Comment

Hodgkin's lymphoma is a curable disease in the majority of cases. However, the rate of relapse varies between 10–15% in stage I-II disease and 30–50% in advanced disease [4]. Risk factors for relapse include: B symptoms, mediastinal involvment, age more than 45 years, male gender, stage IV, more than three nodal sites, bulky disease, and multiple extranodal sites [2,3]. Only a few reports of very late relapses in patients with HL, up to 25 years after first remission, have been published [3]. A second remission is usually achieved in these cases and the prognosis may be better than after an early relapse.

In the last two decades changing patterns of HL relapse have been noted. The incidence of late relapses was higher in patients treated with radiotherapy than among those treated with the combined modality [1,2]. However, patients with stage II disease and those without B symptoms at presentation tended to have more late relapses, justifiyng prolonged clinical and radiologic follow-up. Bodis et al. [2] reported a prevalence of late relapse (up to 15 years) in 3.7% of patients with early stages of HL and a higher incidence of late relapse among patients treated with recent protocols, possibly due to an attempt to tailor therapy to the specific prognostic factors. Among the late relapsers 71% were alive and in complete remission several years after relapse. B symptoms and mediastinal involvement (both present in our patient) were found to correlate with late relapse in this series.

Our patient was first diagnosed and treated in Russia and a possible relation with the Chernobyl accident is possible, although she did not live in an area close to the contamination. The possibility of a second primary HL occurring 17 years after primary diagnosis should be considered in a patient treated with both radiotherapy and chemotherapy even though the similar histology in both occurrences does not support this hypothesis. Molecular tools are available today that may help to differentiate between a relapse and a second primary HL. Since some, but not all, Reed-Sternberg cells are of B origin, the study of the B cell gene rearrangement on single Reed-Sternberg cells could help differentiate reccurence (identical rearrangement) from *de novo* HL (different rearrangement). Similarly, antigen expression, identified by immunohistochemistry, can be useful since divergent antigen expression would suggest *de novo* HL. Recent studies revealed a significant association between the human leukocyte antigen class II allele DPB1*0301 and Hodgkin's lymphoma. Patients carrying this HLA could be at higher risk for developing second *de novo* HL [5].

Unfortunately, tissue from the original presentation 17 years before could not be obtained. Similarly, we could not confirm that the original diagnosis was indeed HL, nodular sclerosis type, and not another histologic subtype of HL. Had the diagnosis been HL, lymphocyte-predominant type, classified today as non-classical Hodgkin's lymphocyte predominant, nodular type, we would have been able to explain the very atypical history of the disease as the clinical course of low grade lymphoma with late relapses.

In patients who survive more than 5 years in complete remission, an increased risk of late relapse has been found to be related to male gender, presence of B symptoms and mediastinal involvement [3]. Initial therapy also influences the incidence of late relapse. Bodis and colleagues [2] found that the more intensive the treatment, the fewer the occurrence of late relapses. Tailoring the treatment according to prognostic factors in early-stage Hodgkin's disease results in lowering the overall risk of relapse, however the probability of late relapses is likely to increase [2].

Our patient is unique because the relapse occurred 17 years after the first diagnosis of HL and combined therapy. Even though she refused therapy for an entire year during which her clinical situation severely deteriorated until she needed prolonged ventilation, her disease was still responsive to chemotherapy and complete remission could be obtained with the conventional ABVD regimen.

In contrast to treatment policies for primary HL, therapy of late and very late relapses of HL has not been extensively investigated due to the lack of large prospective studies. The teatment of choice for patients with early-stage disease relapsing after radiotherapy should include one of the combined chemotherapy regimens used as initial therapy for advanced stages, with a possible cure rate of around 50%. For patients whose initial complete response to chemotherapy lasted more than one year, retreatment with the same regimen offers a long-term survival of 10 years in 45%, but with a high risk of second malignancies [2,4].

Our case shows that very late recurrences of HL of the nodular sclerosis type, 17 years after initial diagnosis and combined therapy, can still be successfully treated, demonstrating that remission and long-term survival are possible.

HLA = human leukocyte antigen

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