Spontaneous regression of primary progressive Hodgkin’s lymphoma in a pediatric patient: A case report and review of literature

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Spontaneous regression of malignancies is a very rare phenomenon. Our research of existing literature yielded only 16 cases of Hodgkin’s lymphoma which regressed spontaneously. The outcome of primary progressive Hodgkin’s lymphoma is poor even with salvage chemotherapy and autologous bone marrow transplantation. Here we present a case of primary progressive Hodgkin’s lymphoma, which regressed spontaneously after failure of salvage chemotherapy. To our knowledge, this is the first case report of primary progressive Hodgkin’s lymphoma undergoing spontaneous regression.

Hodgkin’s lymphoma is a cancer of the immune system that is marked by the presence of Reed-Sternberg cells. It usually has excellent prognosis with five-year survival rates exceeding more than 80%. But the outcome of patients with primary progressive Hodgkin’s lymphoma (PPHL), defined as progression during induction treatment or within 90 days after the end of treatment, is dismal. The complete response (CR) and long term disease free survival (DFS) – with second line chemotherapy in a case of PPHL – is 0–10% respectively.1,2 Even with salvage chemotherapy and autologous stem cell transplantation, five-year overall survival (OS) for these patients is 43%.3

Spontaneous regression (SR) of cancer is the complete or partial disappearance of a malignant tumor without treatment or in the presence of therapy that is considered inadequate in exerting a significant influence on neoplastic disease.4 SR in patients with Hodgkin’s lymphoma is extremely rare. Here we report a case of PPHL in a child who underwent spontaneous regression after failure of salvage chemotherapy. We believe this is the first such case reported in the literature.

CASE REPORT

A 10-year-old girl presented to us in September 2009 with history of fever and cough of two months’ duration. On examination, she was malnourished with height of 118 cm weight of 18 kg and body mass index of 12.9 kg/m².2 The patient had right level 4 lymph nodes measuring 1 cm × 1 cm and splenomegaly of 3 cm below left costal margin. Her chest X-ray showed mediastinal widening (mediastinal to thoracic ratio of 0.4). Cervical lymph node biopsy was diagnostic of Hodgkin’s lymphoma, of the nodular sclerosis type, which was latent membrane protein 1(LMP 1), CD 15 and CD 30 positive (Figure 1a and b). Contrast CT chest revealed multiple mediastinal lymphadenopathies with the largest right paratracheal lymph node measuring 3.7 cm × 3.6 cm. Contrast CT
of abdomen revealed retroperitoneal lymph nodes with mild splenomegaly. The patient’s hemoglobin was 70 g/L, with total white cells $8.7 \times 10^9$/L (neutrophils 75%, lymphocytes 20%, monocytes 4%, and basophils 1%). She had a platelet count of $399 \times 10^9$/L. Her total serum protein was 61 g/L with albumin of 36 g/L, and lactate dehydrogenase was 1120 U/L. Her bone marrow biopsy did not show any lymphomatous involvement (Figure 1c). She was diagnosed with Hodgkin’s lymphoma, nodular sclerosis stage 3B and was planned for six to eight cycles of chemotherapy.

She was started on COPP/ABV (cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine) chemotherapy in October 2009 and completed a total of eight cycles of COPP/ABV chemotherapy in May 2010. At the end of the treatment, she had bilateral axillary lymph nodes of 1 cm $\times$ 1 cm and bilateral inguinal lymph nodes which measured around 1.5 cm $\times$ 1 cm. PET scan revealed increased uptake in above mentioned nodes and also sclerotic lytic lesions in D5, D6, D9, L1 and L5 vertebra. There were lytic lesions in the pelvic bone involving bilateral ilium, left acetabulum, and the left femur involving the intertrochanteric region. Bone marrow biopsy showed sheets of atypical lymphoid cells and small area of fibrosis along with numerous Reed-Sternberg cells which were CD 15 and CD 30, positively suggestive of involvement of the bone marrow (Figure 2a and b). The patient was diagnosed as having primary progressive Hodgkin’s lymphoma.

She received four cycles of salvage chemotherapy-DHAP (dexamethasone, high dose cytarabine and cisplatin) from August 2010 to October 2010. After the end of salvage chemotherapy, she had subcentimetric axillary lymph nodes and inguinal lymph nodes. PET scan showed decreased uptake of above mentioned nodes compared to that performed in May 2010 but showed new areas of uptake with a well-defined hypodense lesion in segment 7 of the liver measuring 1.1 cm $\times$ 1 cm, nodes involving prevertebral and retro caval regions and persisting bone lesions (Figure 3a–d). A repeat bone marrow biopsy showed lymphomatous involvement. The patient was briefed regarding further options including

Figure 1. (a) H&E $\times$ 40 lymph node biopsy showing mono-, bi- to multi-nucleated giant cells of the Reed-Sternberg type. (b) IHC $\times$ 40 mono-, bi- to multi-nucleated giant cells showing CD 30 positivity. (c) H&E $\times$ 40 initial bone marrow biopsy before treatment showing normal marrow.

Figure 2. (a) H&E $\times$ 20 bone marrow biopsy after treatment showing numerous Reed-Sternberg giant cells suggestive of Hodgkin’s lymphoma. (b) IHC $\times$ 40 bone marrow biopsy showing CD 30 positive giant cells. (c) H&E $\times$ 40 bone marrow biopsy taken in March 2012 showing normal marrow.
autologous bone marrow transplantation. Parents wanted supportive care only and declined any further chemotherapy. The patient was discharged from hospital in January 2011.

Surprisingly, the patient reported to our outpatient department 14 months later in March 2012 and was absolutely asymptomatic with weight of 25 kg, height of 125 cm, and BMI of 16. On further enquiry, she reported no use of chemotherapy agents from elsewhere or any alternative form of medicine. On examination, she had only subcentimetric bilateral inguinal lymph nodes. PET scan repeated showed complete resolution of the hepatic lesion and all bone lesions. Nodes in the bilateral inguinal region and in the prevertebral and retrocaval regions did not show any metabolic uptake (Figure 4a–d). Bone marrow biopsy was normal (Figure 2c). The patient was kept under close observation and

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**Figure 3.** (a) PET avid lesion in segment 7 of liver (done in 2010). (b) PET avid nodes involving prevertebral-retrocaval region (done in 2010). (c and d) PET activity in left ilium and left ischium (done in 2010).
follow-up. The last follow-up was in January 2013. Clinically, she is free of lymphadenopathy and is attending school regularly.

**DISCUSSION**

Primary regression of cancer was first described by Sir William Osler in the early 20th century.\(^5,^6\) The frequency of spontaneous regression of cancer is estimated to be about 1 per 100,000 patients. Common cancers undergoing spontaneous regression include renal cell carcinoma, malignant melanoma, neuroblastoma, leukemia and non-Hodgkin’s lymphoma.\(^2\) Among the lymphomas, spontaneous regression has been reported mostly in patients with low-grade non-Hodgkin’s lymphoma\(^7,^8\) but some cases of regression among intermediate or high-grade non-Hodgkin’s lymphomas have also been reported.\(^9,^10\)
case report

Although the exact mechanism of SR remains unclear, various mechanisms have been proposed to explain this phenomenon. These include immunologic factors, concomitant infections, hormonal factors, genetic factors, elimination of carcinogens, surgical trauma of the primary tumor, and induction of differentiation. Spontaneous regression of cancer is most commonly attributed to immunological factors.

Drobyski and Qazi suggest that most SR cases in B-cell lymphoma are due to immunological mechanisms. SR following infections suggests that infections trigger immune responses which may cause spontaneous regression. In the post-organ transplant setting, the SR of tumors, which occurs on stopping immunosuppressants, is also indirect evidence for immune induced spontaneous regression. One more important mechanism that has been proposed is cytokine induced spontaneous regression.

SR of Hodgkin’s lymphoma is extremely uncommon and only 16 cases have been reported in the literature. Among the 16 reported cases of SR, most were of the mixed cellularity subtype, while five cases occurred in children following measles infection. However, all five of these patients still required treatment with chemotherapy following the regression.

In four of these cases, spontaneous regression was thought to be due to abscopal effect, which is the regression of lymph nodes that are outside the radiation field. Our patient had the nodular sclerosis type of Hodgkin’s lymphoma and there was no history of serious infections, genetic factors, hormone or radiation exposure which might have caused the spontaneous regression of cancer.

Our patient is a 10-year-old child who is a case of primary progressive Hodgkin’s lymphoma, and who had spontaneous regression of the disease. She is doing well even after a two-year treatment-free period. This case report is a clear example that mechanisms of SR in cancer are still not fully understood but with rapid progress in understanding the disease biology, we hope to find the answer to this unsolved question soon.

CONFLICT OF INTEREST
None declared.

REFERENCES