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CASE REPORT

A difficult diagnosis of Hodgkin lymphoma due to immune thrombocytopenia

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Key Clinical Message

We report a rare clinical presentation of childhood Hodgkin lymphoma with immune thrombocytopenia. Diagnostic biopsy of the abdominal mass was performed after administration of intravenous immunoglobulins, steroids, and platelet transfusion. Concomitant thrombocytopenia complicated the whole diagnosis work up and the initial management of neoplasia.

Keywords

Child, Hodgkin lymphoma, immune thrombocytopenic purpura.

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder rarely found in patients with Hodgkin lymphoma (HL) [1]. ITP can be the only clinical sign and precede the typical presentation of lymphoma by months or years; alternatively it can be concomitant to lymphoma diagnosis [2]. It has not been clarified whether ITP is a paraneoplastic phenomenon or an independent disorder. We report a pediatric case of HL presenting with thrombocytopenia at diagnosis.

Case Report

A 16-year-old boy complained fever and persistent cough unresponsive to antibiotics. Chest X-ray was normal. After 2 weeks skin petechiae and ecchymoses appeared and the boy was admitted to an Infectious Disease Division. Peripheral blood count showed: hemoglobin 11.9 g/dL, platelet $1 \times 10^3/\mu$L, white blood cells $8.5 \times 10^3/\mu$L, neutrophils 87%, lymphocytes 5%. ITP was suspected and intermediate dose methylprednisolone (0.5 mg/kg/day) was administered for 2 days. CT scan showed multiple masses both in the chest and abdomen, enlarged liver, and hypodense areas in the spleen. On admission to our center, clinical examination revealed obesity (weight 125 kg and height 171 cm), diffuse petechiae all over the skin and ecchymoses on upper and lower limbs. No enlarged peripheral lymph nodes were found. Liver and spleen margins were 2 and 2.5 cm under the lower costal limit, respectively. Laboratory investigation confirmed thrombocytopenia (platelet count $10 \times 10^3/\mu$L) with hemoglobin 12.2 g/dL and white blood cells $13.6 \times 10^3/\mu$L. Erythrocyte sedimentation rate measured 104 mm/h, reactive C protein 17.4 mg/dL (n.v. <0.8), lactate dehydrogenase level 1051 IU/L. Liver function tests including albumin, bilirubin, alkaline phosphatase, gamma glutamyltransferase, coagulation parameters, and transaminases as well as serum immunoglobulin (Ig) levels were within the normal range. Viral serology for EBV, hepatitis A, B, and C viruses and HIV as well as autoimmune markers were negative, thus excluding secondary thrombocytopenia. FDG-PET documented high metabolic activity in all the sites evidenced as pathologic

by CT scan. Leukemia/lymphoma diagnosis was suspected. Bone marrow aspirate and trephine biopsy revealed normal cellularity with no evidence of neoplastic infiltration and increased megakaryocytes, a picture compatible with ITP. A tru-cut biopsy of one of the abdominal masses was excluded due to adiposity and, consequently, it was decided to perform a laparoscopic procedure. In order to achieve a safe platelet value, a dose of 30 g of IVIG for two consecutive days was administered before surgery. Platelet rose to 30 × $10^3/\mu$L and two units of platelets were transfused immediately before and during surgery.

Laparoscopy was complicated by copious bleeding and converted to open surgery. Bleeding was soon controlled with no further complications. Due to the need of respiratory and hemostasis surveillance, the patient was transferred to Intensive Care Unit for 5 days. The platelet count fell to 22 × $10^3/\mu$L and intravenous methylprednisolone (1 g daily for 3 days) was administered with a prompt rise of platelet count (204 × $10^3/\mu$L at day 3). Histological report revealed Hodgkin lymphoma, nodular sclerosis type (immunophenotypic profile: CD 30+, CD15+/–, CD20–, CD3–, CD43–, LCA–, EMA–, ALK–). Chemotherapy was started according to AIEOP LH 2004 protocol, which includes 6 COPP/ABV cycles (cyclophosphamide, vincristine, procarbazine, prednisone/adriamycin, bleomycin, vinblastine) followed by involved field radiotherapy. Platelet count showed an asymptomatic second fall to 75 × $10^3/\mu$L during the first course and rose up to normal values without the need of additional treatments. The boy is now in complete remission, with a normal platelet count, 13 months after the end of treatment (Fig. 1).

Discussion

The association of autoimmune diseases with lymphoproliferative ones, non-HL and HL, has already been reported [3, 4]. However, the nature of this co-existence is still unclear also due to the rarity of this phenomenon. Among

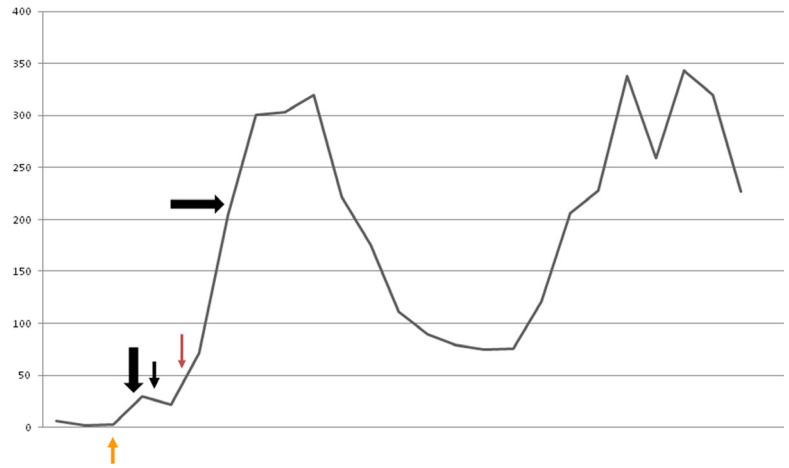

Figure 1. Evolution of the platelet count following treatment. ➡, Chemotherapy; ⬇, Platelet transfusion; ↓, Methylprednisolone; ↑, Immunoglobulins; ⬇, Biopsy.

Table 1. Summary of reported pediatric cases of Hodgkin lymphoma and autoimmune disorders.

Author	Age (years)	Sex	HL stage	AI Disorder	Time of AI disorder onset in relation to HL. diagnosis	AI Disorder therapy	ITP response (days)	AIHA response (days)	HL therapy
Our case	16	M	IIIB	ITP	Precedent	Ig + steroids + Chemotherapy	3	–	COPP+ ABV+RT
Cecinati et al. [16]	16	F	NR	AIHA+ ITP	Precedent	Ig + steroids + chemotherapy	4	5	ABVD
Ertem et al. [17]	6.5	M	IB	AIHA+ ITP	Precedent	Steroids	7	45	OPPA+RT
Shah et al. [18]	4	M	IIIB	AIHA+ ITP	NR	Ig + Trasfusion	3	NR	APE+RT+ OPPA

ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; AI: autoimmune; AIHA: autoimmune hemolytic anemia; APE: cytosine arabinoside, cisplatin, etoposide; HL: Hodgkin lymphoma; Ig: immunoglobulin; ITP: immune thrombocytopenia; NR: not reported; OPPA: oncovin, procarbazine, prednisone, adriamycin; COPP: cyclophosphamide, vincristine, procarbazine, prednisone; ABV: adriamycin, bleomycin, vinblastine; RT: radiation therapy.

autoimmune disorders, the most frequently observed are autoimmune hemolytic anemia and ITP. The prevalence of ITP associated with HL has been estimated at 0.2–1% [5–8]. Among the 4090 HL patients of the British National Lymphoma Investigation Registry, only eight cases of ITP were found [8]. Most reported HL-ITP cases occurred after the diagnosis of lymphoma, even in patients already in remission; in such cases ITP seems to be unrelated to the neoplastic disease [9]. Nevertheless, a large population-based case-controlled epidemiologic study in Scandinavia found a statistically significant increased risk of HL in patients with a history of ITP, suggesting that ITP may precede the onset of HL [10]. The relationship between the two disorders may lead to consider ITP as a paraneoplastic disorder, an erroneous response of the immune system to the uncontrolled malignant cell proliferation or a simultaneous but not related disease [11–13]. Paraneoplastic autoimmune diseases may occur simultaneously with cancer diagnosis or precede it by many years, although it may also be seen after cancer treatment as a sign of recurrence. In those cases where ITP occurrence precedes HL, its persistence until HL detection suggests a specific association between the two diseases [14, 15]. In our case, the immune nature of thrombocytopenia was confirmed by the presence of megakaryocytes in bone marrow aspirate, the poor response to platelet transfusion, the rapid rise of platelet count after administration of steroids, the absence of other clinical conditions that could explain thrombocytopenia such as infections and lupus. Spontaneous remission of ITP during adolescence is not frequent. Therefore, the early ITP remission during the first course of chemotherapy suggests a causative association between the two disorders, with ITP being, therefore, a paraneoplastic phenomenon. This is in agreement with three described pediatric cases where ITP improved after chemotherapy: in all three cases, the autoimmune disorder responded to immune-modulatory therapy (steroids and/or immunoglobulins), with a rapid rise in platelet count, even if chemotherapy was required in order to maintain a stable platelet count [16–18] (Table 1).

Whatever its nature, thrombocytopenia challenged cancer diagnosis: biopsy was postponed in order to achieve a minimum level of circulating platelets, laparoscopy was converted to laparotomy for bleeding, and the patient required hospitalization in intensive care unit. On second thought, more cautious measures could have been adopted: a higher dose of IVIG could have been administrated before surgery, in order to reach a safer platelet count, since steroids were not preferred because their use can complicate diagnosis or its definition. The decision of performing surgery, even with a low platelet count, was due to the diagnostic urgency, but, in such a case, with borderline platelet count, open surgery would have turned out to be a more cautions option. In our case, ITP actually complicated the normal HL diagnostic work up which is usually uneventful, but did not influence the course of antineoplastic treatment.

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Conflict of Interest

None declared.

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