Immune Thrombocytopenia Secondary to Hodgkin's Lymphoma in Children

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ABSTRACT: **Background:** Immune thrombocytopenia (ITP) is an autoimmune disorder of an uncertain origin that results in bleeding and decreased platelet count. Autoimmune abnormalities have been described in patients with malignancies including non-Hodgkin's lymphoma but are rarely described in patients with Hodgkin's lymphoma.

Objectives: To describe an unusual presentation of Hodgkin's lymphoma in an unusual age and alarm pediatricians of the challenging diagnosis.

Methods: We present two cases that highlight an unusual clinical presentation of childhood Hodgkin's lymphoma occurring at a young age.

Results: Over a 4-year period, two children aged 5 and 6 years were admitted for suspected ITP, both had cervical lymphadenopathy. Bone marrow examination showed no evidence of tumor or fibrosis. Biopsy of the lymph node was possible only after administration of intravenous immunoglobulins and normalization of the platelet count. Platelet counts increased after initiation of chemotherapy.

Conclusions: The identification of ITP as a possible presentation of Hodgkin's lymphoma is important to facilitate timely diagnosis and accurate management.

IMAJ 2020; 22: 224–226

KEY WORDS: autoimmune, Hodgkin's lymphoma, immune thrombocytopenia (ITP), paraneoplastic

Immune thrombocytopenia (ITP) is an autoimmune disorder of variable origins that results in bleeding and decreased platelet count. Primary ITP in children is diagnosed by exclusion. ITP can be secondary to infectious diseases, autoimmune diseases, malignancies, or treatment with drugs. Diagnosis of the underlying causes of ITP can be a challenge [1].

Autoimmune abnormalities, such as autoimmune hemolytic anemia and ITP, have been extensively described in patients with malignancies including non-Hodgkin's lymphoma (HL) in both children and adults [2,3], but are rarely described in patients with HL [4-8]. There is mounting evidence that a bidirectional relationship may exist between HL and autoimmune disorders [8-10]. However, there are only a few reports describing pediatric HL and autoimmune disorders at the onset of the disease, most of which occur in teenagers [11-15]. In most of the described cases, the immune manifestations resolved with appropriate HL treatment. Chemotherapy was shown to effectively resolve both the primary malignancy and the autoimmune complications.

In this article, we report on two cases of HL presenting at a young age (5 and 6 years) with an unusual autoimmune complication.

PATIENTS AND METHODS

Over a period of 4 years (2014–2017) a total of 69 children presented to Emek Medical Center pediatric emergency department with initial clinical and laboratory findings suggestive of ITP (well appearing, petechiae, isolated thrombocytopenia, and normal peripheral blood smear). Of these, two children were diagnosed with HL and treated with chemotherapy accordingly. Both children were cured of the lymphoma and had a full resolution of their ITP.

The research was conducted in accordance with the World Medical Association Declaration of Helsinki.

PATIENT 1

A 5-year-old otherwise healthy child was referred to our department with suspected ITP, having noted petechiae and cutaneous hematomas for one week on his hands and legs, without a recent history of trauma, fever, or bleeding from other sites. On admission to the hospital, the patient appeared generally healthy, with no signs of pallor or fatigue. Physical examination was remarkable for scattered hematomas over the arms and legs. Left cervical lymphadenopathy was noted with mobile, non-tender, soft lymph nodes and small bilateral inguinal lymph nodes. No hepatosplenomegaly was noted. On recurrent anamnesis the lymphadenopathy had been present for 3 years with intermittent enlargement and shrinkage. He had

been examined several times during that period, most recently 4 months prior to hospital admission. At that time his blood count was normal and a neck ultrasound demonstrated a 2.2-cm lymph node with clear borders and normal blood flow, which appeared to be reactive. At follow-up, blood count and confirmatory blood smear revealed a platelet count of 6×10^3/ml. Mean platelet volume (MPV) was 16.5 fl with normal hemoglobin and white blood cell count. Repeat ultrasound revealed a collection of enlarged cervical lymph nodes, up to 3 cm in size, which were described as round with hypo-echogenic centers, no evidence of fatty centers, and no abnormal blood flow.

The patient had an excellent response to intravenous immunoglobulin (IVIG) and his platelet count increased to 150×10^3/ml. The histopathological examination of the lymph node disclosed the presence of a classical HL, mixed cellularity sub-type, and bone marrow aspirate was normal. Positron-emission tomography/computed tomography (PET/CT) showed an uptake in the left cervical lymph nodes and the spleen. The patient was diagnosed with stage IIIA HL and treated with the standard protocol of ABVEPC (adriamycin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide). Platelet count returned to normal shortly after the initiation of chemotherapy.

The patient was in complete remission 4.5 years following the treatment with no signs of disease and with normal complete blood count.

PATIENT 2

A 6-year-old otherwise healthy child was admitted to our department due to an abdominal hematoma that appeared after a football game and several spontaneous small scattered hematomas over his body. A few months earlier cervical and submandibular lymphadenopathy had been noticed; however, the patient denied B symptoms (fever, night sweats, and weight loss). Blood tests, including complete blood count (CBC), chemistry, lactate dehydrogenase, and uric acid, were normal. Ultrasound revealed an enlarged posterior cervical lymph node 1 × 3.4 cm in size with normal shape, texture, and blood supply. The child was examined by a hematologist and scheduled for repeat ultrasound.

At admission the patient appeared generally well, with no sign of pallor or fatigue. Physical examination was remarkable for scattered hematomas and purpuras all over his body, a large hematoma on the right abdomen, left cervical, and submandibular lymphadenopathy was noted with mobile, non-tender soft lymph nodes, and no hepatosplenomegaly.

CBC demonstrated a platelet count of 5×10^3/ml. MPV was 18.2 fl, with normal white blood cells and hemoglobin. Repeat ultrasound revealed a large number of enlarged cervical lymph nodes bilaterally as well as nodes in the parotid and sub mandibular regions. Nodes up to 3.5 × 1.8 × 2.2 cm in size were found, with a diffusely thickened cortex, fatty central sinus, and enhanced blood circulation. Abdominal ultrasound revealed an enlarged spleen of 10 cm with multiple small round scattered hypoechogenic lesions. The largest lesion was 2 cm in radius and was located in the lower lobe of the spleen. These findings were confirmed on abdominal magnetic resonance imaging which also demonstrated multiple isointense lesions in T1 and hypointense in T2, with large lesions showing slight diffuse enhancement with gadolinium. The patient had an excellent response to IVIG and platelet count increased to 137×10^3/ml. The histopathological examination of the lymph node disclosed the presence of a classical HL, nodular sclerosis grade 1, associated with Epstein-Barr virus. Bone marrow aspirate demonstrated mild erythroid and megakaryocytic hypoplasia with no evidence of lymphoproliferative disorder. PET/CT showed a high level pathological uptake in the left cervical and para-pharyngeal lymph nodes, bilateral uptake in the nasopharynx and pathological uptake in the upper frontal mediastinum. Moreover there were multiple uptakes in hypodense lesions in the spleen, and an uptake in several lymph nodes in the liver area. The patient was diagnosed with stage IIIs HL and treated with OEPA (vincristine, etoposide, prednisone, doxorubicin) + COPDAC (cyclophosphamide, vincristine, prednisone, dacarbazine) regiment. Platelet count returned to normal soon after initiation of the chemotherapy.

The patient was in complete remission 2.5 years after diagnosis, with no evidence of disease and normal CBC.

RESULTS

Over a period of 4 years a total of 69 children were diagnosed with ITP, in two cases the underlying cause was HL. The thrombocytopenia responded to standard ITP therapy and the patients achieve full resolution of their thrombocytopenia shortly after initiation of chemotherapy.

DISCUSSION

The relationship between autoimmune disorders and lymphoproliferative malignancies has been studied in adult patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia [16].

A French study examining this relationship found various autoimmune disorders in 11 children with HL and the disorders were associated with increased morbidity and mortality [17]. A Scandinavian population-based case control study of HL and autoimmunity reported statistically significant increased risk of HL associated with personal histories of several autoimmune conditions, including ITP [9].

In a study by Lechner and Chen [10], 11 adult patients (mean age 52 years) with HL presented with ITP. This occurred predominantly in males, and a higher than expected frequency of mixed cellularity and advanced disease was observed in these patients compared to the standard population of patients with HL.

In registries from the United States and Europe, HL in young children is very rare with an estimated incidence of

Table 1. Reported cases of immune thrombocytopenia and Hodgkin's lymphoma

Year	Author	Age, in years	Sex	Hodgkin's lymphoma stage	Autoimmune disorder	Initial platelet count	Timing of autoimmune disorder	Days until response	Autoimmmune therapy
2020	Tanous et al. (this article)	5	Male	IIIA	ITP	6	Precedent	5	IVIG
		6	Male	IIIs	ITP	5	Precedent	9	IVIG
2015	Marino et al. [7]	16	Male	IIIb	ITP	1	Precedent	3	IVIG + steroids
2012	Cecinati et al. [15]	16	Female	NR	AIHA+ ITP	76	Precedent	4	immunoglobulin + transfusion + steroids + chemotherapy
2000	Ertem et al. [12]	6.5	Male	IB	AIHA+ ITP		Precedent	7	steroids
1996	Shah et al. [11]	4	Male	IIIB	AIHA + ITP		Not reported	3	immunoglobulin + transfusion
1972	Rudderseet al. [6]	17	Female	IIIA	ITP	10	Subsequent	no response	transfusion + steroids

AIHA = autoimmune hemolytic anemia, HL = Hodgkin's lymphoma, ITP = immune thrombocytopenia, IVIG = intravenous immunoglobulin

1–2 per million children compared to around 29 per million in adolescents, although in developing countries there appears to be a trend toward a younger age. In a Saudi cohort 18.7% of all pediatric HL cases occurred in children younger than 5 years old with a male predominance and mixed cellularity subtype, similar to our patients. No autoimmune disorders were reported [18]. An Italian study demonstrated better outcomes in very young HL patients (younger than 7 years of age) compared to older children [19]. An Israeli study demonstrated a persistent increase in the age-standardized incidence rate of HL in all age groups but most notably in young adults [20]. A study of HL in southern Israel comparing Bedouin and Jewish patients found Bedouin patients to be younger, with a male predominance, and a more mixed cellularity subtype [21].

CONCLUSIONS

ITP as the presenting symptom of HL is rarely described in children, especially at a young age. From the few mentioned cases [Table 1], HL seems to respond to standard therapy for newly diagnosed ITP and tends to remit entirely with chemotherapy treatment for HL. Further longitudinal studies are needed to understand the long-term outcome in such cases.

Acknowledgement

The authors would like to thank the patients and their families

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