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Pediatric Pulmonary Hodgkin Lymphoma: Analysis of 10 Years Data from a Single Center

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Abstract
Several reports indicate that lungs are the extralymphatic site most commonly affected in patients with Hodgkin lymphoma; however, the data in children are rather limited. This retrospective study aimed to assess the frequency, clinical picture, and the impact on prognosis in children with pulmonary Hodgkin lymphoma, who were diagnosed and treated in a single center during a 10-year period. Pulmonary lesions related to HL: nodules and parenchymal infiltrates with cavitations were found in 3 of 32 (9.4%) patients; in 2 cases these were found as the concomitant manifestation whereas in 1 case as the solitary form (Primary Pulmonary Hodgkin Lymphoma). B-DOPA and MVPP chemotherapy combined with mediastinal and pulmonary irradiation resulted in sustained remissions in all 3 patients, lasting 3, 7, and 64 months, respectively. Lung involvement occurs in up to 10% of children with Hodgkin lymphoma. Primary pulmonary Hodgkin lymphoma is a rare and atypical form of Hodgkin lymphoma; thus is associated with delayed diagnosis which does not seem to affect prognosis. It should be suspected in a child with non-resolving pneumonia and pulmonary parenchymal infiltrates with cavitations.

Key words: pulmonary Hodgkin lymphoma, children, parenchymal infiltrates, lung cavitations

Introduction

Hodgkin lymphoma (HL) is the malignancy that originates from the clonal expansion of malignant Hodgkin and Reed-Sternberg (HRS) cells, which are B-cell-derived elements [1]. Its clinical manifestation is in most of cases restricted to organs and structures belonging to lymphoid system; however, in some patients an extralymphatic manifestation may also occur. It is believed that pulmonary lesions are one of the most common forms of Hodgkin lymphoma's extranodal manifestation, but little is known regarding pediatric patients [2]. The aim of the present study was to assess the frequency, clinical picture, and the impact on prognosis in children with pulmonary HL.

Patients and Methods

The study was performed in accordance with the Declaration of Helsinki for Human Research and the study protocol was approved by an institutional Ethics Committee. Records of all patients admitted to the Clinic of Pediatrics, Hematology and Oncology were reviewed and confronted with records of patients studied at the Department of Pathology and the Department of Radiology of the Pomeranian Medical University in Szczecin, Poland. All diagnoses were based on histological as well as immunohistochemical examination according to REAL/WHO classification [3]. Clinical staging was performed according to Ann Arbor staging classification modified by results of the Cotswold consensus meeting [4, 5]. Patients were treated with the use of HD 97 Protocol recommended by the Polish Leukemia/Lymphoma Study Group, designated to decrease late complication of radiotherapy [6]. The follow-up time ranged from 10 to 115 months (mean 65.4, median 59 months). Due to small numbers, statistical evaluation was not performed except of basic descriptive statistics to characterize patients and Kaplan-Meyer method to calculate event-free and disease free survival of patients.

Results

Between January 1, 2000 and December 31, 2009, thirty two children: 13 girls and 19 boys aged 3-17 (mean 12 years, median 13 years) were diagnosed in our institution with HL. The characteristics of patients are given in Table 1.

All patients achieved remission and are off treatment. Only 1 relapse occurred in a male, stage IIB, NS I patient, 3 years from diagnosis. After a median follow-up time of 59 months the probability of event-free and disease free survival is 0.96. Pulmonary lesions related to HL were found in 3 of 32 (9.4%) patients:

(1) Patient KR: a 13-year-old boy with the history of fever, malaise, weakness, loss of weight, and recurrent upper respiratory tract infections. On physical

Table 1. Demographic and clinical characteristics of children with Hodgkin lymphoma.

Sex	13 girls, 19 boys
Age	3-17 years
Histologic subtype (REAL/WHO Classification)	LP – 1 NS – 24 (NS – 4; NS I – 16; NS II – 4) MC – 7
Clinical stage	IIA – 9
(Ann Arbor system)	IIB – 5 IIIA – 4 IIIB – 5 IVA – 2 IVB – 7
Extranodal manifestation (lungs)	3 patients
Treatment	HD-97 Protocol (Polish Leukemia/Lymphoma Study Group; see ref. 16).
Follow-up time	10-112 months

examination he was found to have a painless right cervical lymphadenopathy. A chest X-ray revealed an anterior mediastinal mass whereas a lung CT scan revealed also pulmonary nodules as well as multiple lung cavitations that were not visible on conventional chest radiograms (Fig. 1A, B). Cervical lymph node biopsy confirmed the diagnosis of HL, nodular sclerosis type I. The patient was classified as stage IVB and treated with 8 alternate blocks of B-DOPA and MVPP. He also received mediastinal (25 Gy) and pulmonary (12 Gy) irradiation. All pulmonary lesions resolved after third block of chemotherapy. The patient is now off treatment 64 months from diagnosis and still remains in the first remission.

(2) Patient KH: a 16-year-old boy who was referred to our Department with a six-months lasting history of sacro-coccygeal arthralgia of unknown origin. The chest X-ray performed prior to admission was normal. On physical examination no abnormalities were seen. Chest CT revealed mediastinal enlargement and small nodular lesions in the lung parenchyma (Fig. 2A, B). Mediastinal and open lung biopsies were performed, both revealing HL, mixed cellularity type. The patient was diagnosed as stage IVA and treated according to HD-97 Protocol. He received 8 alternate blocks of B-DOPA and MVPP followed by mediastinal (15 Gy) and pulmonary (12 Gy) irradiation. Pulmonary lesions resolved after the second block of chemotherapy. The patient remains in first remission, 3 months off treatment.

(3) Patient PM: a 13-year-old-boy admitted to our Department with 2 month lasting history of cough, malaise, fever and recurrent respiratory tract infections. Chest X-ray performed 4 weeks prior to admission was suggestive of atypical pneumonia and/or tuberculosis. Tuberculosis was excluded; however, he was treated with several antibiotics with no clinical response. Subsequent chest X-ray

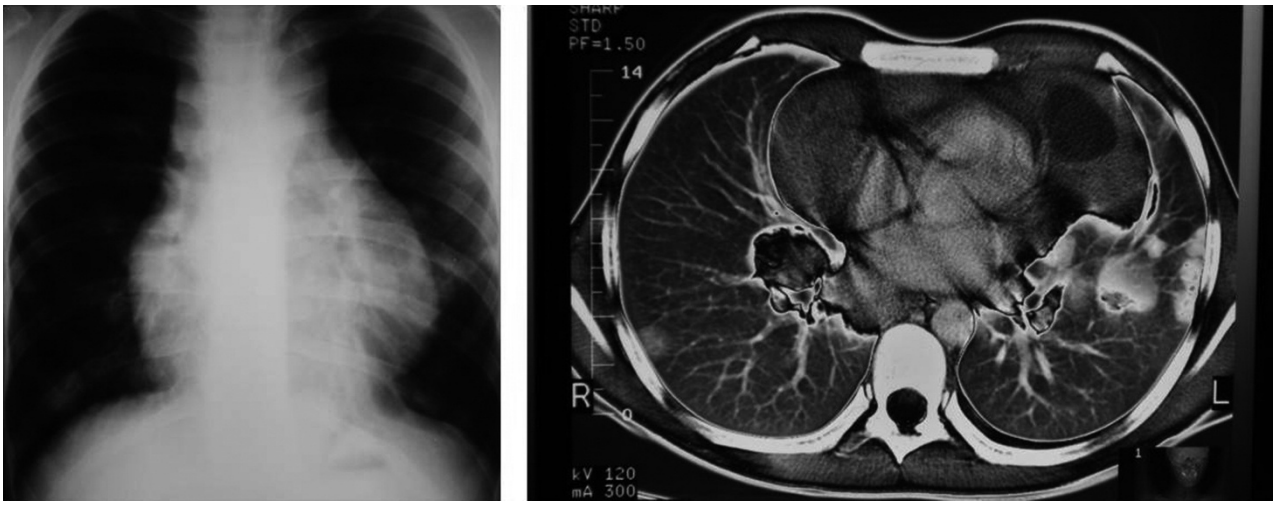

Fig. 1. Patient K.R. A - Chest X-ray showing an anterior mediastinal mass; and B - the lung CT scan showing large parenchymal infiltrates with cavitations.

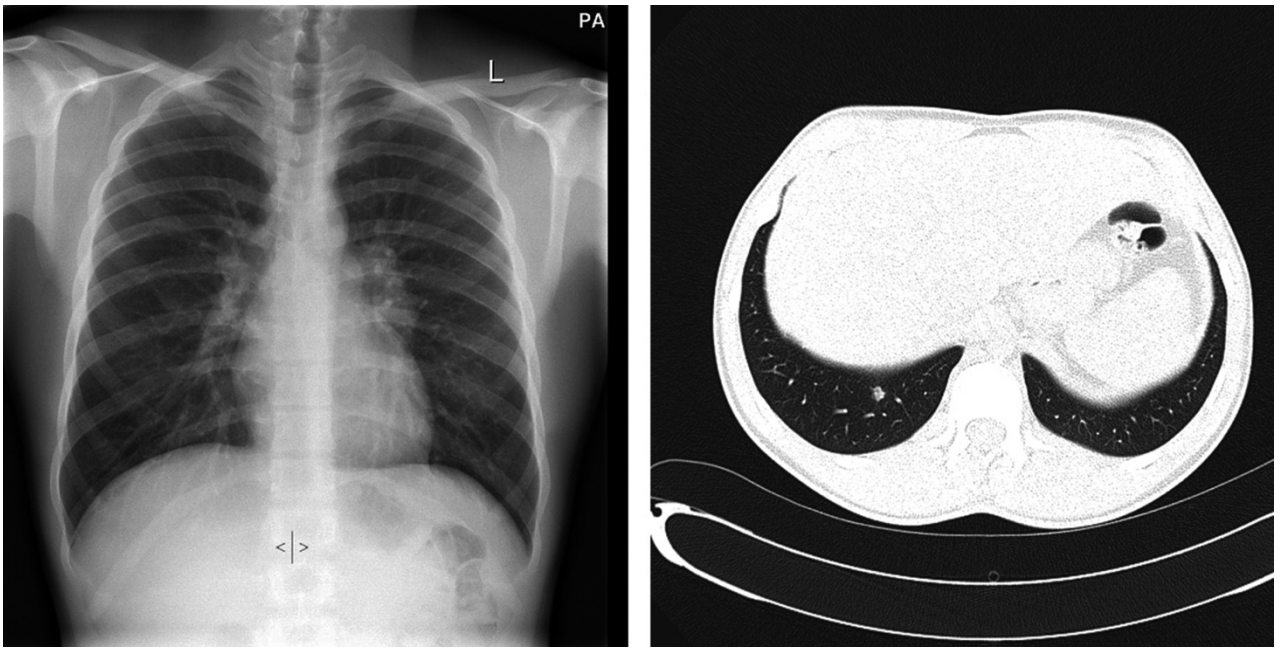

Fig. 2. Patient K.H. A - Normal plain chest film, and B - the lung CT showing pulmonary nodules.

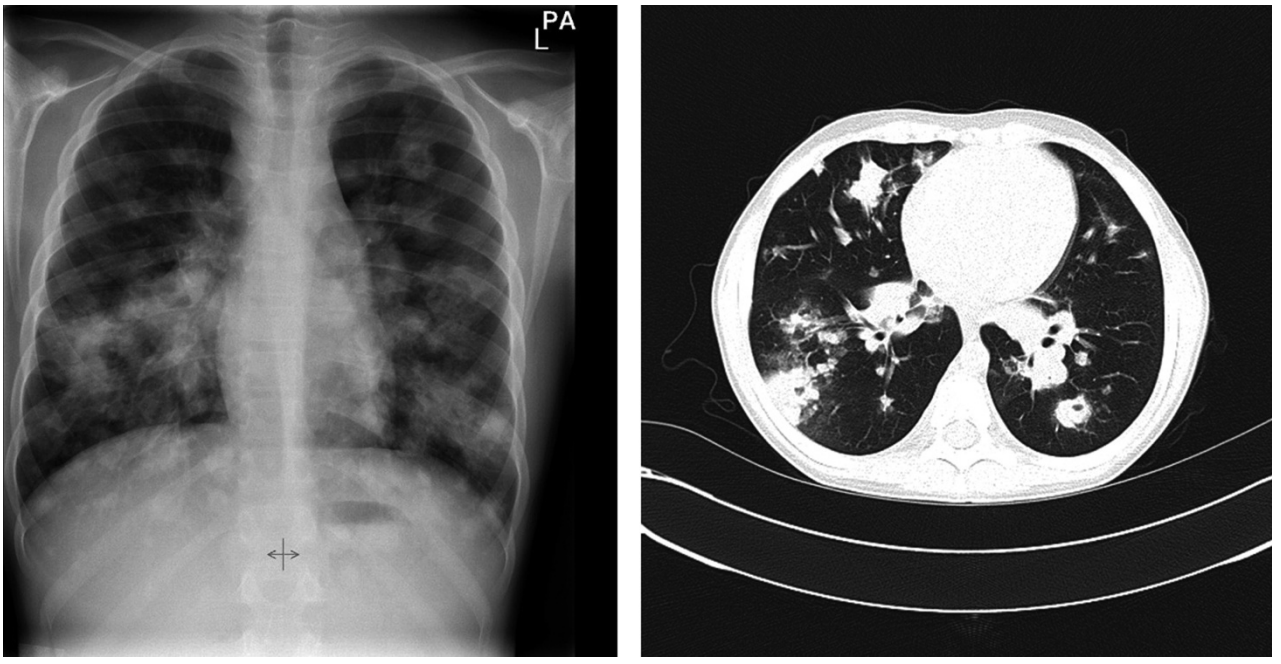

Fig. 3. Patient P.M. A - Chest X-ray; and B - the lung CT scan showing large parenchymal infiltrates with cavitations.

revealed nodular lesions in lungs parenchyma. CT scan showed several irregular infiltrates of both lungs, some of them with cavities (Fig. 3A, B). Bronchofiberoscopy was not diagnostic; thus an open lung biopsy was performed and lesions' specimens were diagnostic for HL, nodular sclerosis. He received eight alternate blocks of B-DOPA and MVPP chemotherapy with pulmonary (12 Gy) and mediastinal (15 Gy) irradiation. He remains in the first remission and off treatment for 7 months. Pulmonary lesions resolved after the third block of chemotherapy.

All these 3 patients have achieved remission and remain in remission and off treatment 3, 7, and 64 months respectively.

Discussion

HL is a form of pediatric cancer that is characterized by excellent prognosis, even in advanced stages of the disease. On the other hand, the prognosis for children with refractory or relapsed disease remains poor [7]. Moreover, it is well known that some forms of treatment used in pediatric HL are associated with serious

late complications, including second malignancy. Current treatment strategies aim to optimize therapy by identifying risk factors which allow to select those who require treatment intensification, whereas low risk patients should benefit from less intensive treatment resulting in a lower rate of late complication [7, 8].

Any unusual manifestation of HL may result in the delay of final diagnosis and a more advanced stage of disease, thus influencing the prognosis. In the majority of pediatric patients clinical manifestation is restricted to the lymphoid system; however, it may occur at any site. There are reports on HL involving urinary tract, even though these cases are extremely rare and occur almost exclusively in adults [9]. There are also reports on osseous involvement in pediatric HL patients, and reports on rare presentation in the central nervous system in children with HL [10-12].

It is commonly accepted that in patients with HL lungs are the extranodal site most frequently affected; however, the rate of this complication in pediatric population is not precisely known, since not all children with HL have chest CT [13]. As it has been reported by Rostock et al [2], 50% of previously untreated patients had intrathoracic disease discovered on CT that had been missed on plain films. This was also the case in two of our patients. Our data indicate that with the use of chest CT scan, the rate of pulmonary involvement in pediatric HL may be as high as 8-10%. With the advent of more sensitive and less harmful imaging techniques like Positron Emission Tomography (PET) this rate will undoubtedly raise.

Pulmonary Hodgkin disease may occur in one of two forms: either as concomitant (Pulmonary Hodgkin Lymphoma; PHL) or solitary (Primary Pulmonary Hodgkin Lymphoma; PPHL) manifestation of HL; the second form being least frequent. Clinical presentation may vary from asymptomatic (pulmonary lesions discovered on imaging studies) to respiratory distress with persistent cough as the most common manifestation [14]. If assisted by lymphadenopathy and/or anterior mediastinal tumor, lymphoma should be always suspected. The diagnosis is based on imaging studies which reveal lung parenchymal lesions: parenchymal pulmonary masses (nodules) and pulmonary cavitations; Hodgkin lymphoma should always be considered in the differential diagnosis of cavitary pulmonary lesions, especially those refractory to treatment [15, 16]. Lesions are unspecific; thus histology is required to confirm the final diagnosis.

Even more difficult is the diagnosis of solitary lung involvement. Isolated involvement of the lung in HL without hilar adenopathy or disseminated disease is a distinct entity and is referred to as primary pulmonary Hodgkin's lymphoma (PPHL) [17]. Pediatric cases of PPHL seem to be extremely rare; within the last 10 years only a few reports have been published. These reports reflect the scope of clinical signs and symptoms: from fever, weight loss and the suggestion of tuberculosis to non-resolving pneumonia diffuse and cavitary lung lesions [15, 18-20]. A misleading clinical manifestation resulted in delayed diagnosis in all reported patients, as well as in a patient presented in this report.

In 1961, Kern et al [21] proposed criteria for establishing the diagnosis of primary pulmonary HL: (1) anatomic documentation of typical histological features of HL; (2) disease restricted to the lung, without or minimal hilar lymph node involvement; and (3) adequate clinical and/or pathologic exclusion of disease at other sites. The first criterion is the most difficult since it requires sampling of the lung tissue. There are reports that in some patients, cavitating consolidation of the lungs are accompanied by endobronchial nodules so these patients may benefit from diagnostic bronchoscopy [20]. In the present study, bronchoscopy was performed in one patient, but it failed in establishing the final diagnosis. Fine needle aspiration biopsy is another diagnostic option however it may bring misleading results; thus an open lung biopsy should be always considered [17]. In our opinion there is no need for surgical resection of all lesions as a therapeutic maneuver (metastatectomy) as it has been described by Karnak et al [22].

There is no specific treatment for pulmonary HL. Lung involvement is always considered as an extranodal manifestation and classified as stage IV; thus patients with PPHL are treated with the most intensive variant of chemotherapy designed to treat HL. That was also the case in our group: all three patients received eight alternate blocks of B-DOPA/MVPP plus mediastinal and pulmonary irradiation. All of them achieved remission and remain in it being off treatment for 64, 3, and 7 months, respectively. The follow-up is definitely too short to validate the quality of remission. Existing literature data and our observations seem to indicate that in children with PPHL the diagnosis is significantly delayed. The delay, however, does not influence the prognosis in these patients [15, 19, 20].

Conclusions

Pulmonary involvement in pediatric HL is relatively frequent (around 10%) and should be considered in a child with lymphadenopathy and mediastinal enlargement accompanied by pulmonary infiltrates and cavitations. Primary pulmonary Hodgkin lymphoma (PPHL) in children is a rare clinical entity of unspecific manifestation which results in delayed diagnosis. It should be suspected in a child with non-resolving pneumonia and/or pulmonary infiltrates with cavitation. The prognosis for children with PPHL is as good as for all children with stage IV HL.

Conflicts of interest: No conflicts of interests were declared by the authors in relation to this article.

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