

Case Report:

Digital Clubbing and Hodgkin Disease in Children: A Case Report and Review of Literature



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ABSTRACT

Introduction: Digital clubbing (hypertrophic osteoarthropathy) as the initial presentation of lymphoma is rarely reported, particularly in children. In this study, we report a patient with intrathoracic Hodgkin Disease (HD) and digital clubbing as the first presentation, and we will review the literature regarding the same condition.

Case Presentation: A 10-year-old boy presented with a 2-month history of cough, mild dyspnea, and night sweats, with prominent digital clubbing. A chest x-ray and a computed tomography scan of the chest showed multiple mediastinal masses. A mediastinal lymph node biopsy was done. Pathologic examination was indicative of nodular sclerosis HD.

Conclusions: In patients with digital clubbing, intrathoracic malignancies should be considered a differential diagnosis and must be ruled out by precise examination and paraclinical help.

1. Introduction

Digital clubbing (hypertrophic osteoarthropathy) is characterized by an increase in nail plate convexity, with focal and bulbous enlargement of the distal phalange, resulting

in a pestle-like appearance of the fingers and toes. It could be associated with various diseases, such as infections, inflammatory disease, cyanotic heart disease, and primary or metastatic pulmonary malignancies [1]. Although the association of digital clubbing with lung cancer is known, it is rarely reported in lymphoma pa-

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tients [2]. Hodgkin Disease (HD) is a malignant tumor with the origin of B lymphocytes [3]. It has a broad spectrum of symptoms and signs; the most common one is painless lymphadenopathy. Also, asymptomatic mediastinal masses are common. B symptoms are relatively frequent, more in adults [4]. Children with HD usually have unspecific presentations, B symptoms, lymphadenopathy, and fever [5, 6].

Although HD is rare in pediatric patients (5% to 6% of all childhood cancers), it accounts for 40% of all lymphomas among children [7, 8]. Hodgkin's lymphoma is rarely associated with clubbing [9]. Herein, we report a patient with digital clubbing as the first presentation of intrathoracic HD.

2. Case Presentation

A 10-year-old boy was referred with a 2-month history of cough, mild dyspnea, and night sweats. The patient had been treated outpatient several times and had partially recovered. Because of the duration and severity of the symptoms, the patient was referred to a pulmonologist with the possible diagnosis of pneumonia. The pulmonologist noticed prominent clubbing of the patient's fingers in the examination. A chest x-ray was taken, which showed a mediastinal mass. According to the digital clubbing and mediastinal mass, the patient was referred to the third-level hospital.

Past medical history, drug history, and family history were unremarkable. The examination upon admission showed a central temperature of 37°C, pulse rate of 80 beats per minute, the respiration rate of 18, and blood pressure of 110/70 mmHg.

In the examination of general appearance, there was no sign of peripheral cyanosis. No peripheral lymphadenopathy was detected, and hepatosplenomegaly was absent in physical examination. Breathing sounds were completely clear in both lungs. Most notably, clubbing of the hand and foot fingers was noticed (Figure 1). Chest x-ray showed a lobulated-shaped opacity at the right para-cardiac zone and a round-shaped opacity at the left parasternal zone (Figure 2A).

Initial hematology assessment showed white blood cell count of $8.2 \times 10^3/L$ with a neutrophil proportion of 72% and the lymphocyte proportion of 28%, hemoglobin level of 11 g/dL, platelet count of $322 \times 10^9/L$, serum ferritin level of 67 ng/mL, lactate dehydrogenase level of 480 U/L and raised C-reactive protein (57 mg/L). The first-hour Erythrocyte Sedimentation Rate (ESR) was 65

mm/h. No abnormalities were found in liver function tests, renal function tests, and blood glucose level. Coagulation tests were normal.

Immunology assessment showed that Cytomegalovirus (CMV) IgG level (82.2 IU/mL) and Epstein-Barr Virus (EBV) IgG level were positive (750 U/mL). But, EBV IgM level, CMV IgM level, Human Immunodeficiency Viruses (HIV), and toxoplasma IgG and IgM were negative.

Hormone analysis showed normal levels of β -human chorionic gonadotropin and α -fetoprotein. Computed Tomography (CT) scan of the chest showed lymphatic masses in the mediastinum (Figure 2B). CT scans of the brain, neck, abdomen, and pelvis were unremarkable.

Based on the patient's symptoms and signs, a mediastinal lymph node biopsy was done. The pathology report and immunohistochemistry staining were positive for CD30 and CD15 and negative for CD45, supporting nodular sclerosis of HD. Chemotherapy was started for the patient. After 6 courses of chemotherapy, mediastinal masses and symptoms were resolved entirely.

3. Discussion and Literature Review

We made a computer-assisted search of PubMed, EMBASE, Google Scholar, and Wanfang databases from 1970 to June 2020 using the keywords "digital clubbing and intrathoracic Hodgkin lymphoma or Hodgkin disease". We also searched some other related keywords, such as "cancer", "lymphoma", "pathogenesis", "clinical presentations", "treatment", and "outcome".

The case presentations, radiographic findings, diagnoses, management, and patient outcomes are described briefly in Table 1. Including our case, 11 patients were analyzed. They consisted of 3 females (27%) and 8 males (73%). The Mean \pm SD age of the patients was 13.18 \pm 2.8 years, with a minimum age of 8 years and maximum age of 18 years.

The patient's clinical presentations were digital clubbing with pain (2 patients) or without pain (1 patient), weight loss (4 patients), fever (2 patients), night sweats (2 patients), cough (5 patients), dyspnea (3 patients), painful arthritis (2 patients), neck mass (3 patients), fatigue (1 patient), hemoptysis (1 patient), and abdominal pain (2 patients).

Radiographic findings were mediastinal lymphadenopathy (6 patients), mediastinal mass (3 patients), lung mass with cavitation (1 patient), and pleural effusion (1



Figure 1. Digital clubbing

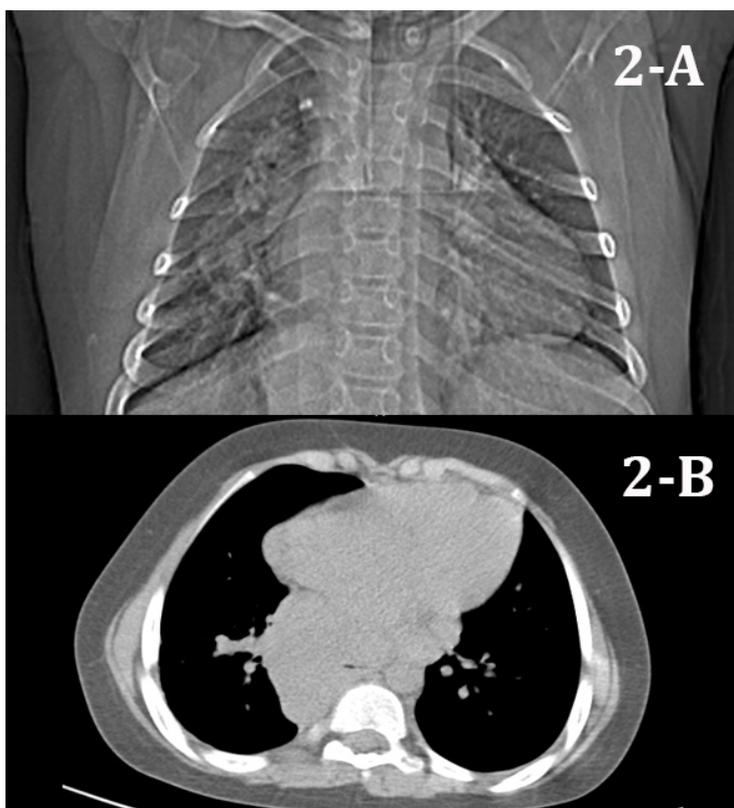
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patient). According to the clinical finding, the patients underwent biopsy with different procedures, including lymph node biopsy (6 patients), thoracotomy (2 patients), CT-guided lung biopsy (1 patient), mediastinoscopy (1 patient), autopsy (1 patient), and not available (1 patient).

Pathology reports confirmed the diagnoses, which were nodular sclerosis (6 patients), mixed cellularity (3 pa-

tients), and lymphocyte depletion (1 patient). In one case, details of the pathology report of HD were unavailable.

Seven patients responded to treatment with chemotherapy and radiotherapy, leading to complete remission of digital clubbing, 2 patients died, and treatment outcomes of the 2 patients were not available.



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Figure 2. A large mediastinal mass in chest X-ray (2A) and thoracic computed tomography imaging (2B) of the patient

Table 1. Pediatric Hodgkin disease Patients with digital clubbing since 1970

Author (Year)	Gender	Age (y)	Dominant Presentations	Radiographic Findings	Pathology Report	Response to Treatment
Goodyer (2009) [10]	Female	18	Weight loss, cough, dyspnea	Mediastinal mass	Nodular sclerosis	Complete remission
Utine (2008) [11]	Male	14	Digital clubbing	Mediastinal mass	Nodular sclerosis	Complete remission
Karadeniz (2001) [12]	Male	8	A mass on the neck, weight loss, night sweats	Mediastinal lymphadenopathy	Nodular sclerosis	Complete remission
Kebudi (1997) [13]	Male	12	Painful digital clubbing	Mediastinal lymphadenopathy	Mixed cellularity	Complete remission
Horak (2002) [14]	Female	12	Cough, fever, hemoptysis	Pulmonary cavitated consolidations	Nodular sclerosis	Not available
Kebudi (2006) [15]	Male	12	Cough, dyspnea, painful digital clubbing, abdominal pain	Mediastinal lymphadenopathy	Mixed cellularity	Complete remission
Kebudi (2006) [15]	Male	16	Fatigue, weight loss, cervical lymphadenopathy	Mediastinal lymphadenopathy	Nodular sclerosis	Complete remission
Adler (1970) [16]	Male	12	A mass on the neck, weight loss	Mediastinal lymphadenopathy	Hodgkin's disease	Expired
Shapiro (1973) [17]	Female	16	Abdominal pain, painful arthropathy	Massive pleural effusion	Lymphocyte depletion	Expired
Shankar (2005) [18]	Male	15	Fever, dry cough, polyarthritits	Mediastinal lymphadenopathy	Mixed cellularity	Not available
Karami (2020) Present case	Male	10	Cough, dyspnea, digital clubbing, night sweats	Mediastinal mass	Nodular sclerosis	Complete remission

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We reported a 10-year-old boy with cough, mild dyspnea, and night sweats for 2 months. Physical examination showed clubbing of the first and second fingers of the right hand and the first, second, and third fingers of the left hand. Chest x-ray and CT imaging showed mediastinal masses. According to the radiologic findings, the diagnosis was assumed to be lung cancer or lymphoma after admission.

Mediastinal lymphadenectomy and biopsy were performed, and the pathology report confirmed the diagnosis of nodular sclerosis HD. In this patient, the tumor was limited to the lymph nodes and had no invasion to the aorta or other mediastinal organs, so the diagnosis was intrathoracic Hodgkin disease. Intrathoracic HD has rarely been reported, and because of its atypical clinical presentation and slow progression, it is usually misdiagnosed at the beginning of the disease [19, 20]. The patient had obvious digital clubbing. If the clubbing is graded from 1 (initial phase) to 5 (Final phase), it was estimated as Grade 4 [1].

4. Discussion and Conclusion

Digital clubbing can be the only presentation or could be a subset of Hypertrophic Osteoarthropathy (HOA).

Hypertrophic Osteoarthropathy (HOA) is a syndrome known by characteristics such as the abnormal proliferation of the skin and bone tissue of the distal extremities. Clinical features of this syndrome are digital clubbing, periostitis of tubular bones, and synovial effusions, mainly in the large joints [21].

HOA syndrome is classified into two types, primary (idiopathic) form and secondary form, which can be associated with other neoplastic, pulmonary, cardiac, gastrointestinal, infectious, endocrine, and psychiatric conditions. Secondary HOA may present with digital clubbing as the only disease presentation or could have the full spectrum of HOA presentations [22].

About 80% of the secondary HOA patients experience pulmonary malignancies (primary or metastatic form). That is why it was known as hypertrophic pulmonary osteoarthropathy before [21, 22]. Digital clubbing is reported more likely in lung cancer patients with Non-Small Cell Carcinoma (NSCLC) type than Small Cell Carcinoma (SCLC) type [23, 24].

Sridhar et al. reported 111 patients with lung cancer, of whom 32 patients had digital clubbing as the clinical presentation (29%). In that report, 35% of NSCLC patients

and 4% of SCLC patients had clubbing [23]. Although the association between digital clubbing and pulmonary neoplasms is known, lymphoma patients with digital clubbing are reported mostly as case reports.

We searched HD patients with digital clubbing in the literature. In 2009, Goodyear et al. reported an 18-year-old woman with cough and weight loss as initial symptoms over 2 years [10]. On examination, the patient had prominent clubbing in her fingers and toes. A large mediastinal mass was reported in CT imaging. A video-assisted thoracoscopic surgery and lung biopsy were done. According to the biopsy report, the diagnosis was nodular sclerosis Hodgkin disease. It was considered to be HOA because of the tibia and fibula distal periosteal thickening.

In 2009, Utine et al. reported a 14-year-old boy diagnosed with nodular sclerosis HD [11]. The patient had significant digital clubbing without painful arthropathy. He was treated with combination therapy of radiotherapy and chemotherapy and had made complete remission. In some cases, the patients showed painful arthropathy, with or without joint effusion, which inflammatory arthritis was considered as a differential diagnosis too, and it had to be ruled out [22].

The digital clubbing cause is still a mystery for us [1, 25]. Many hypotheses explained the pathophysiology of digital clubbing, while the most promising hypothesis was offered by Dickinson et al. They argued that the local activation of platelet-endothelial cells could be the trigger of the clubbing process, which leads to an increased release of fibroblast growth factors (such as platelet-derived growth factor) [1, 26]. The pulmonary megakaryocytes go to the distal parts of the limbs and release growth factors there, instead of converting to the platelets at the first site. Tumor tissue produces a releasing factor (vascular endothelial growth factor) for stimulating the digital clubbing and HOA process [1, 22, 26]. HOA involvement can be preceded by isolated digital clubbing [27]. Some studies reported that raised levels of prostaglandin E2 could be associated with digital clubbing and HOA in lung cancer patients [28]. Although the clubbing pathogenesis in lymphoma patients is still unknown, it is assumed that some mediators such as estrogens, circulatory and neurogenic factors, and growth hormones (produced by tumors) have a significant role in the clubbing process by stimulating periosteal growth. These mediators are not cleared from the circulation completely because of pulmonary arteriovenous shunts [1, 11, 12, 29].

Progression or remission of clubbing can be noticed as a prognostic factor for its underlying malignancy [2]. In

2017, Ciment et al. reported a 59-year-old woman with digital clubbing and lung cancer. After complete remission of cancer due to the treatment, digital clubbing completely resolved [30]. In some other cases, digital clubbing can be reversible after successful treatment of the underlying malignancy. These patients experienced concurrent internal malignancy, and most of them have died or have had extensive metastases [1, 10, 11, 12]. Based on the previous findings, hypertrophic osteoarthropathy due to pulmonary malignancies is more common in adults and rarely reported in children. Lung cancers can cause endocrine changes and subsequently abnormalities in the joints, so patients with HD may experience it. In conclusion, although digital clubbing due to HD is rarely reported in children, in all children with digital clubbing, HD should be considered as a differential diagnosis and must be ruled out.

Ethical Considerations

Compliance with ethical guidelines

Written informed consent was obtained from the patient's parents for publication of this case report. This study was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

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