症例報告

# Treatment delays due to similarities between advanced malignant lymphoma and musculoskeletal neoplasms: Report of two adolescent cases.

Erika Hidawa[1,2], Atsuko Watanabe[1], Takashi Fujino[3], Ryuhei Tanaka[1]*

1) Department of Pediatric Oncology, Hematology, Saitama Medical University International Medical Center
2) Department of Pediatrics, Saitama Medical University Hospital
3) Department of Pathology, Saitama Medical University International Medical Center

Although children and adolescents are less prone to cancer, malignancy is one of their main causes of death. The accurate diagnosis of cancer in young people generally takes longer than the aged population.

We report two 17-year-old males who had orthopedic disorders in whom the diagnosis of malignant lymphoma was delayed. Our cases took a longer time to reach a correct diagnosis than the median time indicated in previous studies. We speculated that the possible reasons why they needed a longer time to be diagnosed may be due to the notion that most young adults tend to be fairly healthy, and they might be more reluctant to disclose their symptoms to their parents. They might not go to the doctor unless they feel they really need to go.

We would like to emphasize that malignancies should always be considered in differential diagnoses and doctors should pay attention to adolescents' way of thinking and their attitude which are unique to this age group.

*J Saitama Medical University 2017; 44(1): 32-36*
(Received March 13, 2017 / Accepted May 22, 2017)

**Key words:** pediatric cancer, adolescent, diagnostic delay, time to diagnosis, non-Hodgkin's lymphoma

## Introduction

The accurate determination of the primary site and the histological type of malignant neoplasms are of critical importance for their management in clinical settings. However, difficulties in getting this information occasionally occurs, particularly in adolescents and young adults since they rarely suspect cancer by themselves. This results in delays in initiating the appropriate treatment, especially when patients have unusual initial symptoms. Hematological malignancies, particularly malignant lymphomas, can be assumed as traumas or injuries when the patients show conspicuous musculoskeletal manifestations during the first medical examination.

Here, we describe two adolescent patients with advanced malignant lymphoma who, due to their unusual presentation, initially believed they had orthopedic disorders. As a result these patients had significant delays in receiving the appropriate treatment.

## Case report

Patient 1: A 17-year-old Japanese male visited his primary care doctor due to pain in his left thigh. When he revisited a doctor due to worsening pain and abdominal bloating, and he had lost four kilograms over the past two weeks. The doctor subsequently sent him to an orthopedist. After a two- month history of a painful growing mass in his left thigh, he was referred to our hospital. Prior to the referral, the orthopedist took a whole body CT scan that revealed not only a tumor in the thigh, but also large intra-abdominal masses (Fig. 1a, b). The mass in the thigh was biopsied, and a pathological examination indicated primary diffuse large B-cell lymphoma (DLBCL, Fig. 2a, b). Although he was treated with a chemotherapy regimen of the Berlin-Frankfurt-Münster 95 (BFM- 95)[1] and an allogeneic stem cell transplantation, he died of DLBCL one year after diagnosis.

Patient 2: A second 17-year-old Japanese male complained

* Correspondence: Dr. Ryuhei Tanaka, Department of Pediatric Oncology, Hematology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan
Tel: + 81 42 984 4111, Fax: + 81 42 984 4663, E-mail: rytanaka@saitama-med-ac.jp
◯ The authors declare that there are no conflicts of interest associated with the present study.

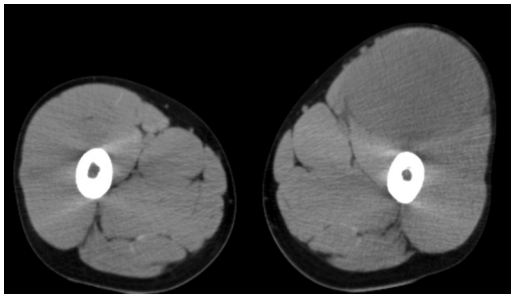

**Fig. 1a.** Axial slice of CT scan: A tumor in the left thigh.

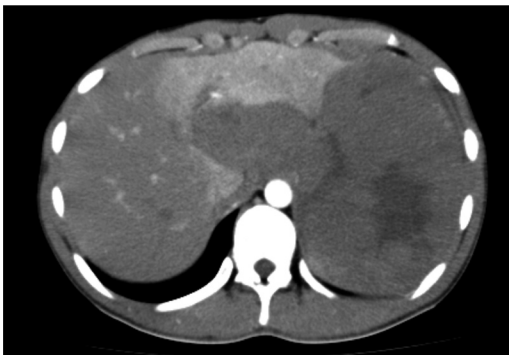

**Fig. 1b.** A large spleen with central necrosis due to lymphoma cell infiltration (b).

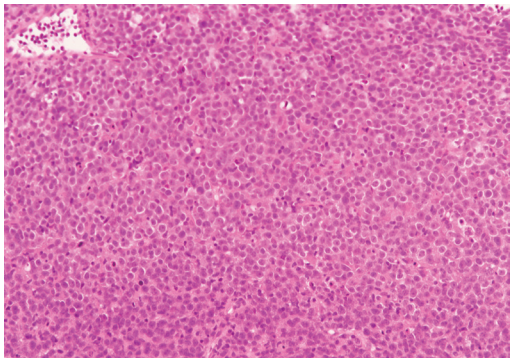

**Fig. 2a.** Histopathological analysis of DLBCL. The tumor tissue from the thigh showed typical large cells (H&E, x200) .

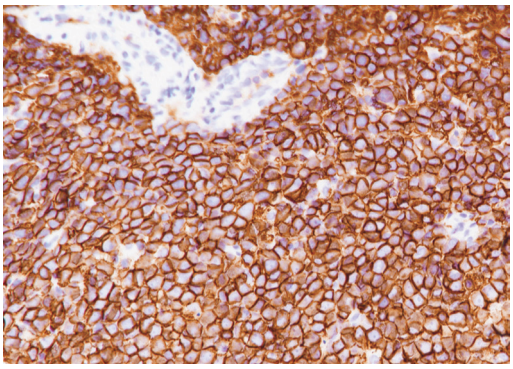

**Fig. 2b.** The cells from the thigh were diffusely positive for anti-CD20 antibody staining (x200).

of pain in the left side of the pelvis. He visited a primary care doctor and had an X-ray examination of his pelvis. At that time, the examination did not reveal any abnormalities. The pain gradually became worse, and he visited the doctor again three months later since he could not walk due to the severe pain. The doctor took an X-ray of the pelvis again and found a significantly large lytic lesion in his pelvic bone that seemed similar to osteogenic cancer (Fig. 3). He was then referred to our hospital, and a chest X-ray revealed a prominent mediastinal mass (Fig. 4). An FDG/PET scan showed that there were multiple lesions in the anterior

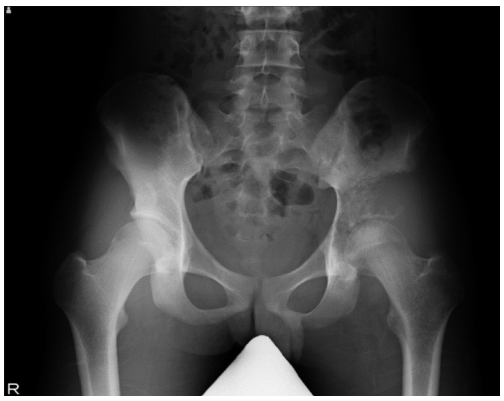

**Fig. 3.** Pelvic X-ray demonstrated lytic lesion in the left hip joint.

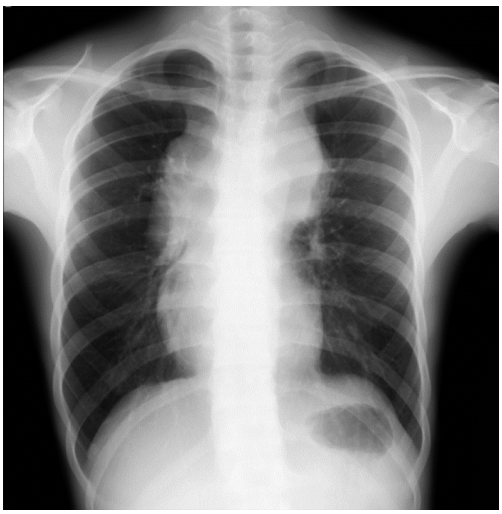

**Fig. 4.** Chest X-ray demonstrated an anterior mediastinal mass.

mediastinum, the right upper pole of the kidney, the hilum of the spleen, and the left coxal bone (Fig. 5). Biopsies were performed on the anterior mediastinal mass and the left coxal bone; both showed typical pathological features of primary mediastinal large B-cell lymphoma (PMBCL, Fig. 6a, b, c). Soon after the biopsy, he had complications with pneumothorax, chest fluid, superior vena cava syndrome and compressed bronchus, and was treated with radiation therapy

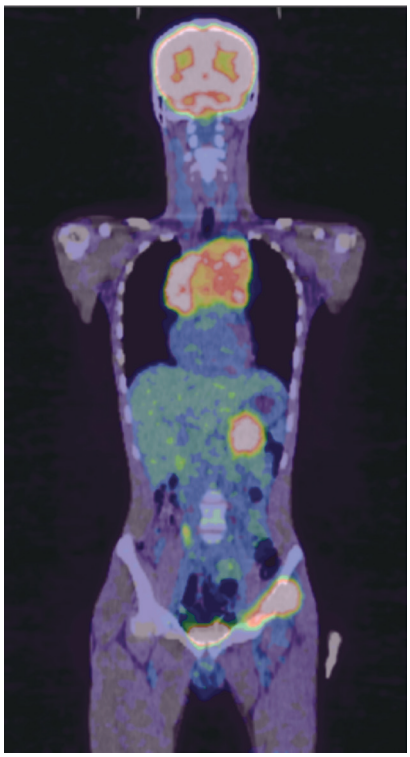

**Fig. 5.** FDG/PET demonstrated multiple masses in the anterior mediastinum, right upper pole of the kidney, hilum of the spleen, and left coxal bone.

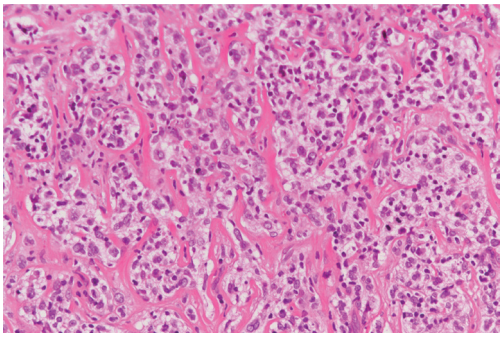

**Fig. 6a.** Histopathological analysis of PMBCL. The tissue from the anterior mediastinal mass showed typical tumor fibrosis (H&E, x200).

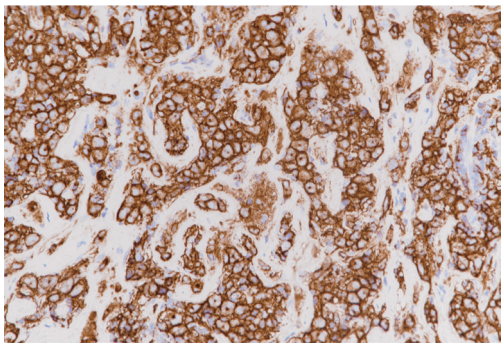

**Fig. 6b.** The cells from the anterior mediastinal mass were diffusely positive for anti-CD20 antibody staining (x200).

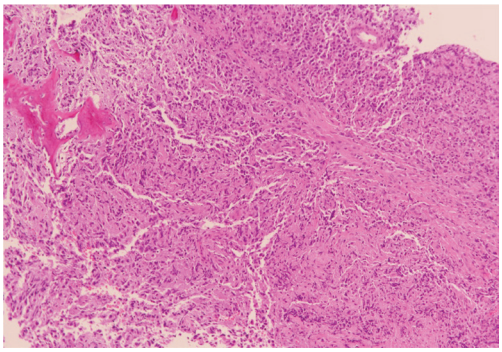

**Fig. 6c.** The cells from the left coxal bone showed the same features as (a). (x40).

followed by cytotoxic therapy. He is currently in complete remission for 6 months after receiving BFM -95.

**Discussion**

In pediatric and adolescent oncology, the median time from the onset of symptoms to diagnosis has not shortened significantly over the past 40 years [2]. This suggests that malignancies in these generations are quite rare, and their diversity and subtle presentations make the diagnosis difficult. Chen and Mullen reported that the median time from symptom onset to diagnosis was the longest for bone tumors (median 86.5 days, 7-1483 days) compared with other type of tumors or tumors in other sites [2]. Brasme and colleagues reviewed the distribution of time to diagnosis in pediatric cancers including non-Hodgkin lymphoma, which has a median of 26.6 days [3]. Pollock and colleagues [4] reported a significantly shorter time to diagnosis of non-Hodgkin lymphoma for patients with an abdominal mass or breathing difficulty compared with those without.

Our two cases took 60 and 75 days to diagnosis. These times to diagnosis were significantly longer than the median time indicated in previous studies [3]. The principal determinants of time to diagnosis for pediatric cancers are age, tumor type, and histology [3]. In both our cases, the lengthy time to diagnosis was due to the first symptoms being atypical and nonspecific. In general, young patients with bone or muscle symptoms are suspected to have orthopedic disorders.

DLBCL often presents in extranodal sites that include the testis, skin, lungs, bone and central nervous system, as well as the respiratory and gastrointestinal tracts [5]. DLBCL arising primarily in the skeletal muscle is exceptionally rare, particularly in the thigh and calf areas [5]. For PMBCL, approximately 50 % of patients have signs and symptoms for superior vena cave syndrome at presentation [6]. Although extranodal PMBCL are common, one of our patients presented with severe pelvic pain, which is an exceedingly rare symptom, but without any other complaints. In addition, malignant lymphoma with bone lesions is unusual and

accounts for approximately 7 % of all bone malignancies [7].

Several studies have shown that for adolescents and young adults, they take longer to diagnose [2]. Because of their psychological factors, patients in this age range may be at higher risk for a delay in diagnosis. They have a strong sense of invincibility; out of denial, they may delay seeing a physician despite their symptoms [8]. Also, they are sometimes too embarrassed to bring the problem to someone's attention. Teenagers tend to be self-reliant and may be more reluctant to disclose their symptoms to their parents; most reports have indicated that children tend to refuse parental surveillance until young adulthood. Furthermore, due to the rarity of these tumors in this population, some of the most advanced cancer presentations occur in this age group [9]. While the impact of time to diagnosis for cancer survival rate is unclear [3], shortening the time to the correct diagnosis may alleviate patients' suffering and improve their survival rate. Since cancer is the second cause of death in children, [10] we strongly believe it is important to consider the way of thinking and attitude of young patients. In addition, seeing a doctor early may help reduce anxiety and distress in patients and their families.

**Acknowledgements**

We would like to thank Dr. Tetsuro Kodaka for his surgical treatments for these two patients.

**References**

1) Möricke A, Reiter A, Zimmermann M, Gadner H, Stanulla M, Dördelmann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. Blood 2008; 111: 4477-89.
2) Chen J, Mullen CA. Patterns of diagnosis and misdiagnosis in pediatric cancer and relationship to survival. J Pediar Hematol Oncol 2017; 39(3): e110-5
3) Brasme JF, Morfouace M, Grill J, Martinot A, Amalberti R, Bons-Letouzey C, et al. Delays in diagnosis of paediatric cancers; a systematic review and comparison with expert testimony in lawsuits. Lancet Oncol 2012; 13: e445-59.
4) Pollock BH, Krischer JP, Vietti TJ. Interval between symptom onset and diagnosis of pediatric solid tumors. J Pediatr 1991; 119: 725-32.
5) Bourdeanu L, Menon R, Somlo G. Diffuse large B-cell lymphoma with calf muscle localization. Case Report in Hematol 2011; 2011: 292494.
6) Savage KJ. Primary mediastinal large B-cell lymphoma. Oncologist 2006; 11: 488-95.
7) Unni KK. Malignant lymphoma. World Health Organization Classification of Tumours. Lyon, France: IARC press; 2002; 306-8.
8) Archie B, Ronald DB. Cancer in Adolescents and Young Adults. In: Archie B, Karen HA, Albritton, Lynn AG, Ronald DB. Introduction: Diagnosis, signs and symptoms. New York: Springer; 2007. P. 15-6.
9) Lethaby CD, Picton S, Kinsey SE, Phillips R, van LM, Feltbower RG. A systematic review of time to diagnosis in children and young adults with cancer. Arch Dis Child 2013; 98: 349-55.
10) Health, United States, 2015. In: Leading causes of death and numbers of deaths, by age: United States, 1980 and 2014 Available via: http://www.cdc.gov/nchs/hus/contents2015.htm#020. Accessed Dec. 31, 2016

# 骨格筋系の症状で発症する全身性の思春期悪性リンパ腫では診断が困難ないし遅延しやすい：最近の２症例の経験から

飛田和　えりか[1,2)]，渡辺　温子[1)]，藤野　節[3)]，田中　竜平[1)*]

1) 埼玉医科大学国際医療センター　小児腫瘍科

2) 埼玉医科大学病院　小児科

3) 埼玉医科大学国際医療センター　病理学

悪性リンパ腫は，小児と思春期における代表的な悪性腫瘍のひとつである．若年者におけるがん罹患者数は少ないが，悪性疾患はこの年代における死因の上位である．しかし，一般的に若年者の悪性疾患を迅速かつ的確に診断することは，高齢者に比較し時間を要することが多いと言われている．実際，我々は最近，整形外科的疾患を疑わせる症状を契機に見いだされた 17 歳男性の悪性リンパ腫 2 例を経験したが，確定診断に到るまでに相当の時間を要していた．その要因として，思春期の心理的特性，特に，自分自身の健康への過信や両親に自分の体調について細かく伝えるようなことはしなくなる，といった年齢相応の思考と行動パターンが強く影響していると考えられた．それは海外の同様の検討結果のそれよりも長時間であった．悪性疾患専門病院紹介に至るまでの過程を検討すると，思春期患者特有の思考と行動パターンが一因と考えられた．若年者に限らないが，実地診療では必ず悪性疾患を鑑別に挙げる必要があるとともに，思春期患者特有の思考と行動パターンを考慮する必要があると考える．

 