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Case Report

Positron Emission Tomography/Computed Tomography False Positivity for Xanthogranulomatous Inflammation in an Adolescent with Hodgkin's Lymphoma

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Abstract.

Although positron emission tomography/computed tomography (PET/CT) is a sensitive tool for Hodgkin's lymphoma (HL) staging and response evaluation, its role in early detection of disease relapse remains controversial. A high false positivity of routine PET/CT during follow-up may result in unnecessary treatment of HL patients who are in complete remission. Here we report a 15-year-old boy who had a false positive PET/CT result during his follow-up. Debulking surgery was performed for the suspicious lesion, which showed xanthogranulomatous inflammation, fibrosis, old hemorrhage and fibrous adhesion of thymic tissue and pleura, but no residual tumor cells. One year after the surgery, this patient remained well without any evidence of disease relapse. Our case shows that PET/CT could provide false positive imaging in HL patients who are in complete remission after treatment. Tissue biopsy remains the really necessary tool of confirming disease relapse in patients with HL.

Keywords **:** Hodgkin's Lymphoma, PET/CT, false positivity

病例報告

罹患何杰金氏淋巴瘤青少年以正子電腦斷層攝影偽陽性為表現的黃色肉芽腫性發炎

俞瑞庭 [1,2]　滕傑林 [1,3,4]　林瑛珠 [1]　王任卿 [5]　黃文豐 [1]*

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中文摘要

雖然正子電腦斷層攝影對何杰金氏淋巴瘤的分期及評估治療反應為一相當敏感的工

具，但針對早期發現疾病復發的角色仍無定論。因正子電腦斷層攝影用於常規追蹤時有較高的偽陽性，容易導致已有完全緩解的患者接受不必要的治療。我們報告的病例是一位 15 歲少年，於接受正子電腦斷層攝影追蹤時發生了偽陽性。腫瘤減積手術的病理報告發現有黃色肉芽腫性發炎（xanthogranulomatous inflammation）、纖維化、陳舊出血、及胸腺與肋膜的纖維沾黏，但卻沒有殘餘癌細胞。經手術一年後，該患者仍恢復良好、沒有疾病復發的跡象。這個病例說明了正子電腦斷層攝影用於治療後已達完全緩解的何杰金氏淋巴瘤患者追蹤時可能發生偽陽性，因此組織切片仍是何杰金氏淋巴瘤患者在確認疾病復發時的主要依據。

關鍵字: 何杰金氏淋巴瘤、正子電腦斷層攝影、偽陽性

INTRODUCTION

Positron emission tomography/computed tomography (PET/CT) is widely used for staging, response evaluation and disease recurrence detection in Hodgkin's lymphoma (HL) [1]. As compared with conventional evaluation, PET/CT provides more accurate staging and strong prediction of treatment outcome. According to a prospective study conducted by Hutchings et al. [2], PET/CT has a higher diagnostic accuracy than CT in HL staging. Compared with CT, 16% of patients are upstaged by PET/CT. On the contrary, only 5% of patients are downstaged. The change of disease stage leads to different treatment strategies in 7% of patients. A recent study by El-Galaly et al. [3] proposes that PET/CT staging may help to omit routine bone marrow biopsy, which does not change the risk assessment or treatment strategy. Also, many previous studies [4] have demonstrated that patients' surveillance PET/CT is more predictive in both progression-free survival (PFS) and overall survival (OS) after treatment of HL. However, a high false positivity of routine PET/CT during follow-up seems to be a challenge, which might result in overtreatment to HL patients who are in complete remission. Herein, we present a 15-year-old boy who had a false positivity of PET/CT after successful treatment of his HL.

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CASE REPORT

A 15-year-old boy, without any inherited diseases or other previous systemic diseases, presented with productive cough for one month, accompanied by poor appetite and night sweats. His body weight decreased from 86 to 79 kilograms in two months as well. Physical examination showed no neck, axillary, or inguinal lymphoadenopathy. His liver and spleen were not palpable. Laboratory examinations showed leukocytosis (27,000/mm^3; normal range, 4,000-11,000/mm^3), an elevated erythrocyte sedimentation rate (64 mm/hr; normal range, 0-15 mm/hr), and normal liver and renal functions. However, computed tomography (CT) of the chest demonstrated a large hypervascular tumor in the left anterior mediastinum, which was about 11.5 cm in maximal diameter. Several small lymph nodes within 2 cm were also found in the upper mediastinum. A sonography-guided biopsy of the mediastinal mass revealed nodular sclerosing Hodgkin's lymphoma (Figure 1A), which was positive for CD30 (Figure 1B) and CD15 (not shown), but negative for CD20 (Figure 1C), immunohistochemically. Gallium-67 scintigraphy confirmed the results obtained from CT (Figure 2). Bone marrow examination presented no evidence of lymphoma involvement. He was diagnosed to have Hodgkin's lymphoma, stage IIX.

For his stage IIX HL, he started to receive two

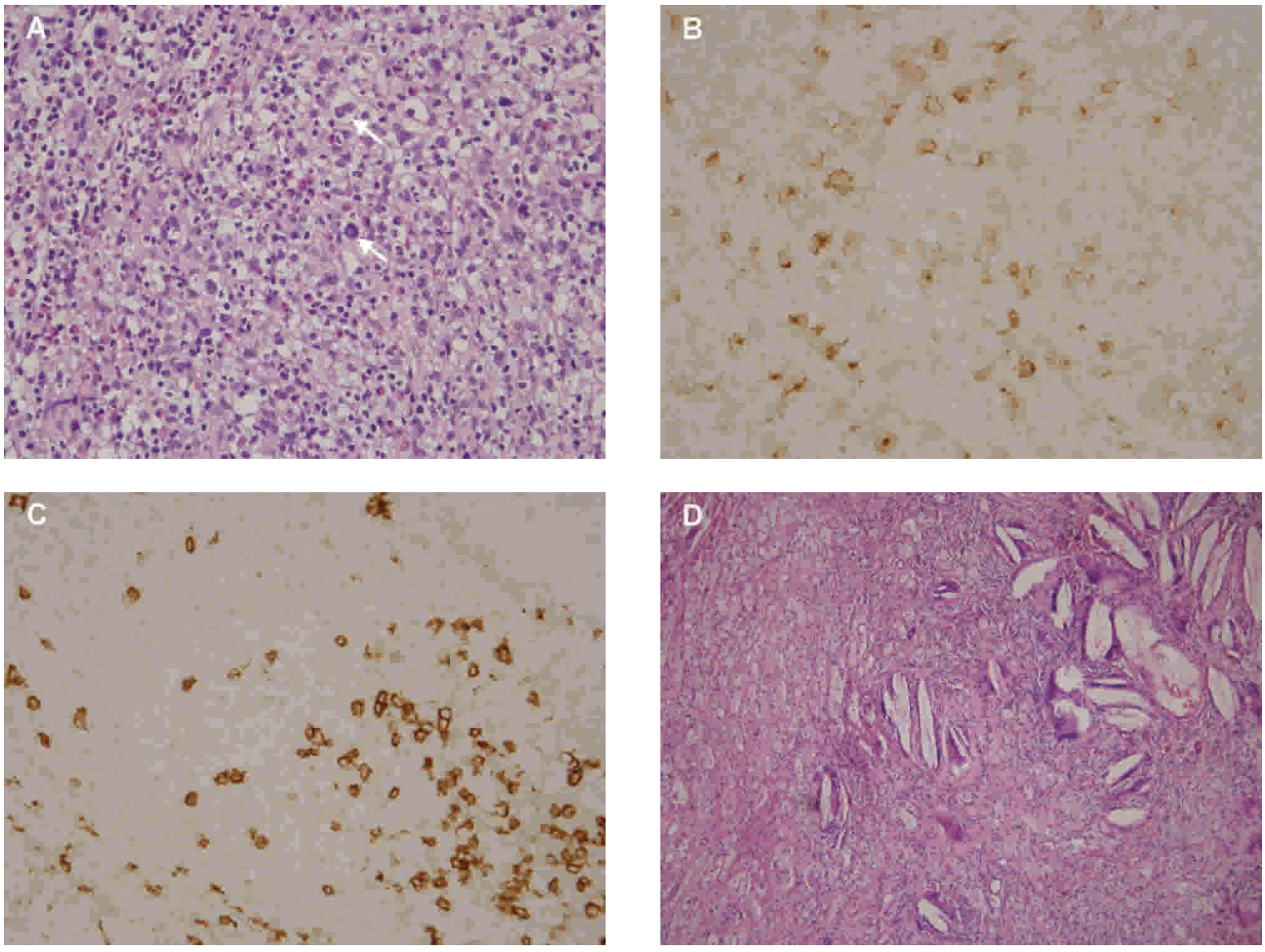

Figure 1. A. Hematoxylin-eosin (H&E) stain showing inflammatroy background, mixed with neutrophils, small lymphocytes and eosinophils. Scattered infiltration of large cells (arrows) with large round to oval nuclei were also seen (original magnification x 400). B. Immunohistochemical staining showing positive CD30 with membranous and focal para-Golgi apparatus pattern of those large cells (original magnification x 400). C. Only small lymphocytes in the background stained positive by CD20 (original magnification x 400). D. H&E stain showing xanthogranulomatous inflammation, cholesterol cleft, fibrosis, and old hemorrhage, but no residual tumor cells (original magnification x 100)

cycles of chemotherapy with the ABVD regimen (doxorubicin 25 mg/m^2, bleomycin 10 U/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2, day 1 and day 15, every 4 weeks). Thereafter, interim PET/CT showed an increased ^{18}F-fluorodeoxyglucose (FDG) uptake in the left mediastinum, with a maximal standard uptake value (SUV_{max}) of 11.8 at 1 hour. This PET/CT also demonstrated increased FDG uptake on both sides of the neck and in both axillary regions (the highest SUV_{max} of 10.5 at 1 hour). Because of partial response, we continued another four cycles of chemotherapy with the ABVD regimen. After completing a total of six cycles of chemotherapy with the ABVD regimen, CT of the chest was performed, showing residual tumor, which was about 7 cm in maximal diameter. With a SUV_{max} of 6.7 at 1 hour in the left mediastinum, subsequent PET/CT showed only partial regression. Moreover, a new FDG uptake was found

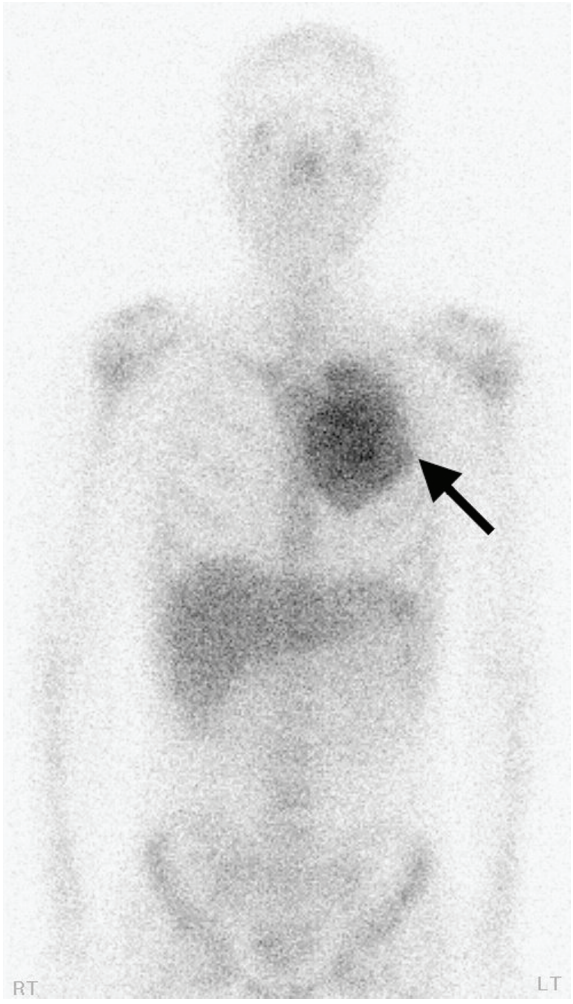

Figure 2. Gallium-67 scintigraphy showing increased uptake in the left upper thoracic region (arrow)

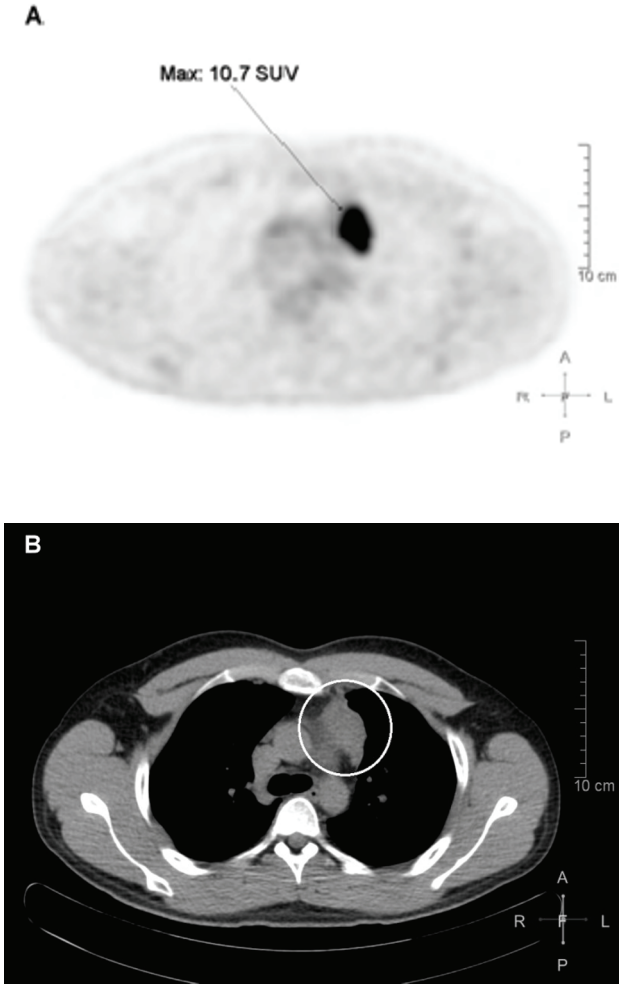

Figure 3. Positron emission tomography/computed tomography showing a lesion with FDG uptake in the left mediastinum, with SUV_{max} of 10.7 at 1 hour (Panel A and B)

in the upper mediastinum. The SUV_{max} was 6.3 at 1 hour. The new lesion from PET/CT suggested early relapse.

Salvage chemotherapy with the ICE regimen (ifosfamide 5 g/m^2 for one day, day 2; carboplatin AUC 5 for 1 day, day 2; etoposide 100 mg/m^2 over 3 days, day 1 to day 3) was performed. After three cycles of chemotherapy with the ICE regimen, the patient received autologous hematopoietic stem cell transplantation conditioned by the BEAM regimen (BCNU 300 mg/m^2 for 1 day, day -6; etoposide 150 mg/m^2 over 5 days, day -5 to day -2; cytarabine 200 mg/m^2 over 5 days, day -5 to day -2; melphalan 140 mg/m^2 for 1 day, day -1). After successful engraftment occurring on Day 9, the follow-up CT of the chest showed only partial remission. For residual disease, he received a 27 Gy intensity-modulated radiotherapy. Unfortunately, the previous FDG uptake did not change significantly. As the patient was free of symptoms, he received close observation but no further treatment.

Table 1. Comparison with published studies for positron emission tomography in follow-up of HL patients

References	Patients	Sensitivity	Specificity	PPV	FP	NPV
El-Galaly et al. [16]	161	100%	82%	22%	17%	100%
Lee et al. [17]	192	100%	92%	23%	8%	100%
Levine et al. [18]	34	100%	84%	11%	16%	100%
Crocchiolo et al. [19]	27	100%	70%	54%	30%	100%

PPV, positive predictive value; FP, false positive rate; NPV, negative predictive value

He received another CT of the chest eight months after radiotherapy, which showed tumor size reduction. However, a lesion with a size of 4.3 x 2 cm remained. Moreover, PET/CT showed the SUV_{max} of 10.7 at 1 hour and 14.3 at 3 hours in this area (Figure 3), consistent with disease in progression. As the HL was considered to be in progression, debulking operation for the mediastinal tumor with video-assisted thoracoscopic surgery was performed. Surprisingly, the pathological findings consisted merely of xanthogranulomatous inflammation, fibrosis, old hemorrhage and fibrous adhesion of thymic tissue and pleura. No residual tumor was found (Figure 1D). One year after the surgery, this patient remained well without evidence of disease relapse.

DISCUSSION

With modern therapy, Hodgkin's lymphoma can now be cured in more than 90% of patients with early HL, and 70% in cases of advanced HL [5]. However, long-term complications for treatment have contributed to the patients' mortality and morbidity, and the complications include early cardiovascular diseases, pulmonary dysfunction, and secondary malignancies [6]. Thus, HL needs a careful approach, since optimal treatment with efficacy and acceptable toxicity is extremely important. As compared to many approaches, PET/CT is now widely used for staging, response evaluation and relapse detection in patients with HL [1]. The guidelines from the National Comprehensive Cancer Network recommend routine surveillance with PET/CT for initial staging and final response evaluation in patients with HL [7]. The role of PET/CT in disease interim evaluation and early detection of relapse disease, however, remains controversial.

A reduction in tumor size on CT is the most dominant conventional methods for treatment response monitoring [8]. However, the malignant cells occupy only a small fraction of tumor volume in HL. Most of the remaining cells are reactive infiltrating cells, which are not directly affected by antitumor therapy [9]. Therefore, size reduction alone may not be an accurate predictor for treatment response. Conversely, functional imaging with PET/CT enables early evaluation of the metabolic changes in HL. Hutchings et al. [10] showed a strong association between early interim FDG-PET and patients' PFS ($P < 0.0001$) and OS ($P < 0.03$). A projected 5-year PFS for PET-negative and -positive patients were 91.5% and 38.5%, respectively. In addition, a study conducted by Gallamini et al. [11] further demonstrated positivity of early interim FDG-PET could be of superior prognostic value to the International Prognostic Score in advanced HL.

False positivity of PET/CT during follow-up has been reported in several cases [12-15]. There are also some studies focused on this issue (Table 1). A multicenter retrospective study by El-Galaly et al. [16] showed that the true and false positive rates of routine PET/CT in HL patients who achieved first remission were 5% and 17%, respectively. Since overall positive predictive value (PPV) was only 28%, the cost for each relapses found by routine PET/CT was high. Furthermore, Lee et al. [17] showed that the PPV of PET/CT and that of CT were 22.9% and 28.6%, re-

spectively (P=0.73) in HL patients who were in first remission, and so CT was not inferior.

Based on previous studies, the possible etiologies contributing to false positivity of PET/CT include fibrosis, lymphoid hyperplasia, progressive transformation of germinal centers, abdominal wall hernia, thymic hyperplasia, human immunodeficiency virus-associated lymphadenopathy, and infection/inflammation [15,18,19]. For patients with HL, tumor cells can express a high level of glucose transporter 1 (GLUT1), enhancing glycolytic activity in the tumor cells [20]. Moreover, GLUT1 expression can be observed in transformed germinal centers and hyperplastic follicles, which could be one of the mechanisms responsible for false positive results of PET/CT in our patient. Inflammation was another possibility for false positivity of PET/CT in our patient. The pathological findings from the mediastinal mass showed only benign changes with xanthogranulomatous inflammation (XGI), characterized by a destructive inflammatory process and accumulation of lipid-laden fibrous tissue and inflammatory cells [21]. False positivity of PET/CT has been reported in patients with XGI in the gallbladder and pancreas [22,23]. However, to the best of our knowledge, Hodgkin's lymphoma-associated XGI has never been reported. Further studies are needed to clarify the relation between XGI and false positivity of PET/CT in patients with HL.

In conclusion, we have reported a case of HL with false positivity of PET/CT during follow-up, which might be associated with XGI. Although PET/CT is a useful, sensitive tool for disease staging and response evaluation, tissue biopsy remains the method which is really necessary in confirming disease relapse in patients with HL.

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