# Case Report Systemic progression of primary cutaneous anaplastic large cell lymphoma in <sup>18</sup>F-FDG PET/CT: a case report

Jia Cheng<sup>1,2</sup>, Yongkang Qiu<sup>2</sup>, Lele Song<sup>2</sup>, Jing Wu<sup>1</sup>, Lei Kang<sup>2</sup>

<sup>1</sup>Department of Nuclear Medicine, Zhengzhou Central Hospital Affiliated to Zhengzhou University, Zhengzhou 450000, Henan, China; <sup>2</sup>Department of Nuclear Medicine, Peking University First Hospital, Beijing 100034, China

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Abstract: Primary cutaneous anaplastic large cell lymphoma (pcALCL) is a type of skin T-cell lymphoma with a favorable prognosis. Some patients may experience recurrence, but systemic involvement is rare. Some studies suggest that systemic progression is associated with poor prognosis. The value of <sup>18</sup>F-FDG PET/CT in diagnosing lymphoma has been recognized, but there is often controversy over the application value of <sup>18</sup>F-FDG PET/CT in pcALCL. We present a rare case of pcALCL involving multiple systemic lesions, monitored and evaluated using <sup>18</sup>F-FDG PET/CT to assist in clinical treatment decisions. Through this case, we consider that <sup>18</sup>F-FDG PET/CT has significant value in diagnosing pcALCL. However, more clinical cases are needed to confirm whether high FDG uptake is associated with the invasiveness of pcALCL and the impact of high FDG uptake and Ki-67 expression on the progression and prognosis of pcALCL.

Keywords: Primary cutaneous anaplastic large cell lymphoma, <sup>18</sup>F-FDG, PET/CT, progression, Ki-67

#### Introduction

Primary cutaneous anaplastic large cell lymphoma (pcAL-CL) is a type of primary cutaneous CD30+ lymphoproliferative disorder [1], accounting for approximately 9% of cutaneous T cell lymphoma [2]. Clinical manifestations of pcALCL typically include slow-growing, painless nodules or masses, some of which may be associated with localized lymph node involvement [2, 3]. Most cases have an indolent course, occasionally manifesting with aggressiveness. Spontaneous resolution may occur in some cases, while others may recur [3, 4]. Progression to systemic involvement is relatively rare [5], with multisystem participation even rarer [6]. Herein, we report a locally recurrent pcALCL involving multiple systems throughout the body.

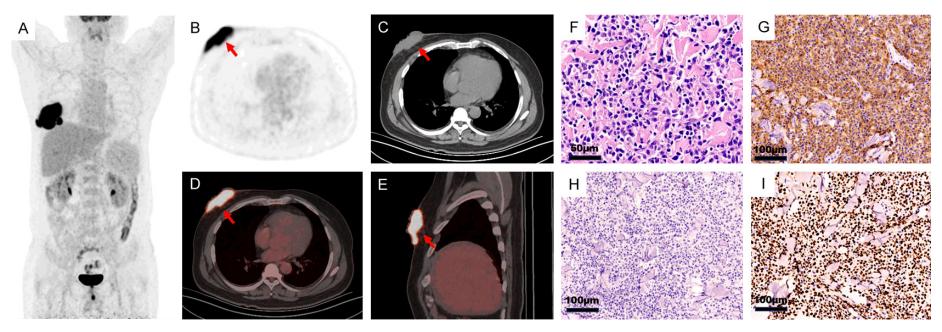
2-Deoxy-2-[fluorine-18]-fluoro-D-glucose (18F-FDG) positron emission tomography combined with computed tomography (PET/CT) as a systemic imaging modality providing both anatomical and metabolic information of lesions has been recognized for its value in the diagnosis, assessment of therapeutic efficacy, and disease monitoring of lymphomas [7]. However, for pcALCL, due to the small and flat skin lesions, <sup>18</sup>F-FDG uptake may be insignificant or lack focal uptake, leading to controversies regarding the value of <sup>18</sup>F-FDG PET/CT [8, 9]. It often demonstrates significant advantages in disease progression or when multiple sites are involved [9]. We now report a case of pcALCL recurrence with systemic involvement, applying PET/CT for continuous dynamic assessment, aiming to provide some reference value for future clinical decisions regarding pcALCL.

#### **Case presentation**

A 45-year-old male was incidentally found to have a tumor below the right nipple on the chest wall about one month ago, measuring approximately 1.5 cm × 1.5 cm in size. There were no local symptoms such as redness, swelling, pain, or skin breakdown, nor were there any systemic accompanying symptoms such as fever or weight loss. Pathological findings after tumor resection revealed diffuse infiltration of medium to large-sized pleomorphic mononuclear tumor cells in the dermis to subcutaneous tissue, with irregular nuclear morphology, eosinophilic cytoplasm, conspicuous mitotic figures, and focal involvement of the epidermis. Immunohistochemical staining showed Vimentin (+++), LCA/CD45 (++), CD43 (++), CD3 (+), CD20 (-), PAX5 (-), CD30 (+++), CD4 (90%), CD8 (10%), ALK (-), CD5 (++), TIA-1 (+), GB (+), MUM1 (++), P63 (+), Ki67 (90%) (Figure 1). Considering the above information, the diagnosis was peripheral T-cell lymphoma, excluding systemic involvement, consistent with primary cutaneous anaplastic large-cell lymphoma [10, 11]. Chest wall MRI showed postoperative changes with no signs of recurrence.

After several months of treatment with interferon and methotrexate, the therapeutic effect was not satisfactory. The tumor on the right anterior chest wall recurred and continued to enlarge and protrude. Eight months later, there was an epidermal breakdown with occasional bleeding, without pain or itching. Eleven months later, <sup>18</sup>F-FDG PET/CT imaging showed soft tissue masses on the right chest wall with increased FDG uptake (**Figure 1**), indicating lymphoma recurrence. Subsequently, after over a





**Figure 1.** <sup>18</sup>F-FDG PET/CT images of a patient after local recurrence in the right anterior chest wall of pcALCL and histological and immunohistochemical characteristics. (A) The wholebody maximum intensity projection showed a high FDG uptake mass in the right anterior chest wall. (B-E) The right anterior chest wall mass showed increased FDG uptake, with an SUV max of approximately 16.5. (F) Hematoxylin-eosin (HE) staining showed that diffuse infiltration of medium to large-sized pleomorphic mononuclear tumor cells in the dermis to subcutaneous tissue, with irregular nuclear morphology, eosinophilic cytoplasm, conspicuous mitotic figures, and focal involvement of the epidermis (magnification, ×400). Immunohistochemical staining showed that tumor cells were CD30 positive (G), ALK-negative (H), and Ki67 90% (I) [magnification (G-I) ×200].

month of local radiotherapy, the tumor significantly decreased in size. Interferon and methotrexate were concurrently administered for treatment.

However, at 13 months, the patient experienced limited back mobility without obvious triggers, accompanied by significant night sweats, and denied discomfort such as pain and fever. Follow-up <sup>18</sup>F-FDG PET/CT scan revealed localized thickening of the skin with increased FDG uptake in the right buttock, enlarged right axillary lymph nodes with increased FDG uptake, multiple low-density lesions in the liver and spleen with increased FDG uptake, numerous areas of FDG uptake in the ribs, sacrum, bilateral iliac bones, right ischium, and left femur, with partial lytic bone destruction (**Figure 2**). Overall, lymphoma involvement in multiple systems was considered.

Ultrasound-guided fine-needle aspiration biopsy of the enlarged lymph node in the right axilla revealed the following pathology: diffuse proliferation and infiltration of medium to large-sized atypical mononuclear tumor cells in the aspirated fibrous tissue, with irregular nuclear morphology, visible mitotic figures, and pathological mitotic images. Immunohistochemical staining showed CD3 (+), CD20 (-), CD30 (+++), ALK (-), CD43 (++), CD56 (-), CD4 (90%), CD8 (10%+), TIA-1 (+), GB (+), CD2 (+++), CD7 (+), and Ki67 (90%) (Figure 3). In situ hybridization showed negative EBV (EBER). Therefore, lymph node involvement is considered to be due to cutaneous anaplastic largecell lymphoma. Bone marrow aspiration found no definite evidence of lymphoma involving the bone marrow. The patient received four cycles of the BV-CHPE regimen chemotherapy (Brentuximab vedotin, Cyclophosphamide, Doxorubicin Liposome, Prednisone, Etoposide), followedup <sup>18</sup>F-FDG PET/CT indicating partial remission (PR) (Figure 4). Subsequently, after continuing with two more cycles of BV-CHPE chemotherapy, <sup>18</sup>F-FDG PET/CT, head MRI, and pre-transplant performance evaluation, autologous stem cell transplantation (ASCT) was performed. After six months of follow-up, the patient showed no obvious signs of disease progression.

### Discussion

The incidence of primary cutaneous CD30+ T-cell lymphoproliferative disorders ranks second among cutaneous T-cell lymphomas, including lymphomatoid papulosis, primary cutaneous anaplastic large cell lymphoma, and borderline lesions, with pcALCL accounting for approximately 9% of all cutaneous T-cell lymphomas [1, 2, 10, 12]. The incidence is relatively higher in males, with an average age of 60 [12]. PcALCL typically presents with an indolent course, with a 5-year survival rate between 85% and 100% [6]. Sarfraz et al. analyzed 501 cases of pcAL-CL reported from 2005 to 2016, with 5-year and 10-year overall survival rates of 80.6% and 61.5%, respectively. The study found that factors such as age  $\geq$ 60 and chemotherapy were associated with survival rates [13]. Accurate clinical diagnosis and staging are the cornerstones of disease management. Pathology is often used as the "gold standard", playing a decisive role in disease diagnosis. However, in diagnosing pcALCL, there is a high correlation between pathology and clinical staging, consideration given only after excluding involvement beyond the skin [10]. It is crucial to differentiate between pcALCL and systemic ALCL secondary skin involvement in disease diagnosis, as they significantly differ in treatment and prognosis. Previously, the expression of the anaplastic lymphoma kinase (ALK) protein was commonly used to distinguish between pcALCL and systemic ALCL, with ALK negativity in pcALCL and positivity in sALCL. However, in recent years, there have also been occasional reports of ALK-positive pcALCL cases [14]. Therefore, differential diagnosis between the two requires comprehensive analysis from histology, IHC, clinical manifestations, imaging, and other aspects. In this case, we only discuss the clinical manifestations, imaging findings, and relevant IHC indicators of pcALCL.

The typical clinical presentation of pcALCL includes solitary, clustered, or multifocal nodules lasting at least 3-4 weeks. Some cases may spontaneously regress or improve, but over half may recur. Approximately 10% may have extracutaneous involvement, with regional lymph node involvement being the most common [15]. However, systemic involvement is rare and often indicates a poor prognosis [5]. Mu HX et al. reported a case of recurrent pcALCL involving the liver, bones, right lung, and widespread lymph nodes [6]. In this case, pcALCL involved a broader range, including lymph nodes, liver, spleen, and multiple bones, particularly the skeletal system, which is extremely rare in previous research reports. Furthermore, skin lesions of pcALCL often involve the head, neck, and limbs, with multiple literature reports indicating a poorer prognosis when lesions affect the skin of the lower limbs [15]. However, in this case, the initial affected area was the trunk.

Imaging examinations are usually required for auxiliary evaluation to determine the extent of the lesion and whether other areas are involved. For extranodal lymphomas, areas such as the gastrointestinal tract, head and neck, lungs, skin, bones, and brain can all be affected [16]. The value of different imaging examinations varies depending on the location of the lesion. For example, for lesions in the cervical region, contrast-enhanced computed tomography (CT) is typically the frontline imaging modality for initial diagnosis, enabling the determination of the extent of the lesion and bone involvement [16]. MRI is often the preferred examination for soft tissue lesions or brain injuries due to its excellent soft tissue contrast [17].

Unlike CT and MRI, <sup>18</sup>F-FDG PET/CT can provide anatomical and metabolic information about lesions, which is essential in evaluating lymphoma [7, **18**]. However, due to

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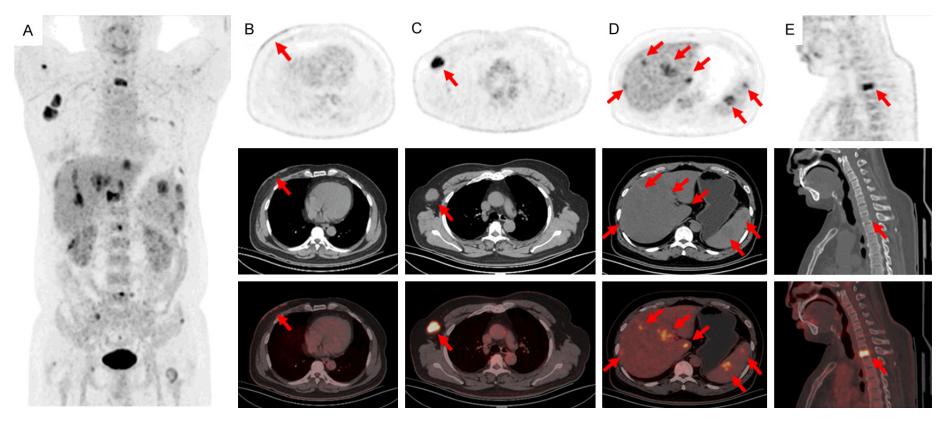
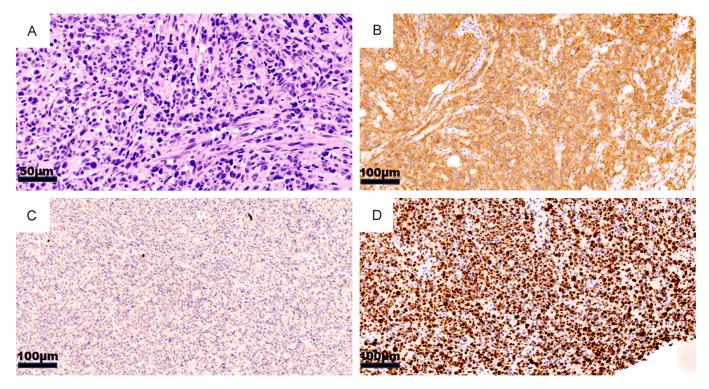
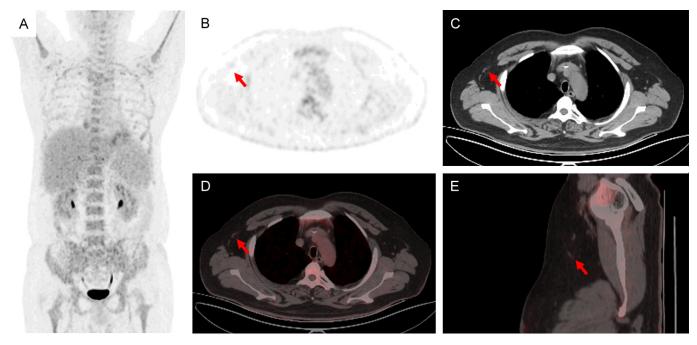


Figure 2. <sup>18</sup>F-FDG PET/CT images of a patient after systemic progression in pcALCL. (A) The whole-body maximum intensity projection showed multiple areas of high FDG uptake throughout the body. (B-E) The anterior chest wall (B), right axillary lymph nodes (C), liver, spleen (D), and bones (E) showed multiple areas of high FDG uptake.



**Figure 3.** Histological and immunohistochemical characteristics of the right axillary lymph node after systemic progression of pcALCL. (A) Hematoxylin-eosin (HE) staining showed that diffuse proliferation and infiltration of medium to large-sized atypical mononuclear tumor cells in the aspirated fibrous tissue, with irregular nuclear morphology, visible mitotic figures, and pathological mitotic images (magnification, ×400). Immunohistochemical staining showed that CD30 positive (B), ALK-negative (C), and Ki67 90% (D) [magnification (B-D) ×200].



**Figure 4.** <sup>18</sup>F-FDG PET/CT images of a patient after treatment for systemic progression of pcALCL. A. After treatment for pcALCL, the whole-body maximum intensity projection showed that most of the multiple areas of high FDG uptake throughout the body have disappeared. B-E. The size and metabolism of the lymph node in the right axilla returned to normal.

the peculiarity of pcALCL, lesions are mostly confined to the skin, with some possibly manifesting only as mild skin thickening [8, 9]. The diagnostic value of PET/CT is controversial, but it still has significant advantages over CT and MRI [19, 20]. In the initial staging study of cutaneous T-cell lymphoma, Ram-Wolff et al. analyzed the sensitivity

of CT and FDG-PET as 18% and 64%, respectively [20]. Compared to the initial diagnostic value of pcALCL, the value of PET/CT in disease monitoring and therapeutic evaluation has been more widely recognized [9, 21, 22]. Casulo et al. suggested that compared to CT, using FDG-PET for midterm therapeutic evaluation could change the clinical stage in 5.2% of patients (5/95). Therefore, they believe that early assessment with PET/CT is necessary for pcALCL [21]. In this case, we used PET/CT to monitor relapse and evaluate the efficacy of pcALCL, providing crucial clinical value for the re-staging and treatment guidance of the disease.

For tumor lesions, the level of FDG uptake is typically associated with the malignancy of the tumor, with some believing that the higher the FDG uptake, the higher the malignancy and risk of progression of the cancer [17, 23, 24]. Makis et al. believe that PET/CT can serve as an essential examination for assessing the invasiveness of pcALCL [25]. In this case, following tumor recurrence, PET/CT scans revealed a significant increase in FDG uptake in the right anterior chest wall mass, with no involvement observed in other parts of the body. After chemotherapy, the mass noticeably decreased in size, but subsequently, the patient experienced systemic involvement, indicating intense tumor aggressiveness. We believe this is consistent with the high FDG uptake characteristics displayed by the tumor on PET/CT imaging. It should be noted that FDG is a non-specific imaging agent that can exhibit high uptake in both inflammation and tumor lesions. Therefore, when evaluating the degree of FDG uptake to assess the condition, it may be necessary to exclude inflammatory lesions based on pathological results.

Meanwhile, we consider the Ki-67 index noteworthy. Ki-67 is unaffected by factors such as age, gender, and clinical stage, and it can objectively reflect the proliferative capacity of tumors [26]. Studies have shown that in non-Hodg-kin lymphoma, there is a positive correlation between SUVmax and Ki-67 expression in PET/CT, so high Ki-67 levels usually indicate strong tumor invasiveness [26, 27]. Mu HX et al. reported a case of systemic progression of pcALCL with high Ki-67 expression, suggesting that a Ki-67 cutoff of 45% can be used to distinguish between indolent and aggressive lymphomas [6]. In this case, we observed that in both immunohistochemical results, the Ki-67 expression of this patient was 90%, which contradicts the indolent nature of pcALCL. The rapid progression course ultimately confirmed its high invasiveness.

Chen et al. found that patients with CD30+ lymphoproliferative disorders of the skin have a much higher risk of developing systemic lymphoma compared to the general population [28]. Therefore, even if pcALCL often presents as an inactive course, we should be cautious, especially when combined with high Ki-67 expression. We must closely monitor changes in the patient's condition to intervene promptly. However, there is no clear report on whether high FDG uptake is associated with the invasiveness of pcALCL, and more cases need to be verified. From this case, we consider that high FDG uptake after excluding inflammatory infiltration also requires us to monitor disease. PET/CT follow-up may provide more excellent clinical value.

In terms of treatment, due to the involvement of lesions predominantly confined to the skin in pcALCL, local surgical excision and radiation therapy are often used as firstline treatment modalities, with systemic chemotherapy being reserved only for cases of multifocal lesions or systemic progression [15]. For recurrent or refractory pcAL-CL, ASCT is also considered an important therapeutic option [29]. A retrospective analysis of ASCT treatment in recurrent ALCL patients found that the 5-year survival rate was 73% for ALK-positive ALCL, compared to only 46% for ALK-negative cases [30]. However, studies by Zhang C et al. have shown that ASCT as salvage therapy can partially improve prognosis and is well-tolerated for recurrent or refractory peripheral T-cell lymphomas [29]. The patient experienced local recurrence, symptom improvement, and systemic progression after undergoing local treatment and systemic chemotherapy. We treated the patient with ASCT. After six months of follow-up, the patient showed no apparent signs of disease progression, but long-term follow-up is still required.

### Conclusion

Herein, we present a rare case of pcALCL progressing from local recurrence to multisystem involvement, highlighting the potential value of PET/CT examination in patients with pcALCL. We consider whether high FDG uptake excluding inflammatory lesions is related to the invasiveness of pcALCL and the value of these characteristics for clinical decision-making, which requires more cases for validation.

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Written informed consent was obtained from the individual.

## **Disclosure of conflict of interest**

None.

Address correspondence to: Lei Kang, Department of Nuclear Medicine, Peking University First Hospital, Beijing 100034, China. E-mail: kanglei@bjmu.edu.cn

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