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Case Report

Primary cutaneous γδ-T-cell lymphoma (CGD-TCL) with unilateral lower extremity swelling as first-onset symptom: a rare case report

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Abstract: Primary cutaneous γδ-T-cell lymphoma (CGD-TCL) is a distinct disease entity which is an extremely rare neoplasm with poor prognosis, characterized by the γ/δ T-cell receptor expression on atypical lymphocytes. We report the case of a 42-year-old man who first presented with a swelling in the extremities and subsequent appeared subcutaneous nodule over the body. In order to clarify the diagnosis, a biopsy of subcutaneous nodule for pathology had been done. CGD-TCL was diagnosed by histopathology, immunophenotype, in situ hybridization and analysis of TCRγ genes rearrangement. The patient was treated with chemotherapeutic regimens-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone). After one period of chemotherapy, subcutaneous nodules became small, even disappeared, swelling and ulcer in the left pedal gone away gradually. One month later after first chemotherapy, tumor relapsed with lesions growing back rapidly, also showed disease in double lungs. The patient was just 10-month survival time from the onset. To our knowledge, this case is the first report of CGD-TCL with unilateral lower extremity swelling as the first-onset symptom. If patient is presented the first symptoms such as swelling of extremities, especially when ulceration appears, it is of great significance to be considerate about the possibility of CGD-TCL.

Keywords: Lymphoma, primary cutaneous γδ-T-cell lymphoma, diagnosis

Introduction

Primary cutaneous γδ-T-cell lymphoma (CGD-TCL) is an extremely rare neoplasm with poor prognosis, characterized by the γ/δ T-cell receptor expression on atypical lymphocytes. CGD-TCL was classified as a provisional entity within the broad category of cutaneous peripheral T-cell lymphomas, unspecified/NOS and rare subtypes in the World Health Organization-European Organization for Research and Treatment of (WHO-EORTC) classification of cutaneous lymphomas [1], and subsequently as a distinct disease entity by the World Health Organization 2008 classification [8]. Subcutaneous panniculitis-like T-cell lymphoma γ/δ subtype (SPTCL-GD) described in previous classification has been replaced by CGD-TCLs now, in order to differentiate from α/β subtype (SPTCL-AB) in clinical, histologic, and immunophenotypic data, treatment, and prognosis.

Case presentation

A 42-year-old man presented with a 5-month history of swelling and slight pain in left foot and ankle, 3-month history of shallow ulcer in left ankle and 4-day history of subcutaneous nodule in the extremities and trunk (**Figure 1**). Skin and soft-tissue infections were initially diagnosed at a local hospital and the patient had no improvement of symptoms with oral antibiotics (amoxicillin) treatment one week. Two months later, the patient first appeared epidermal vesiculation, and then developed into a shallow ulcer on left ankle. Patient visited local hospital again and was diagnosed as systemic vasculitis and hospitalized in local clinic.

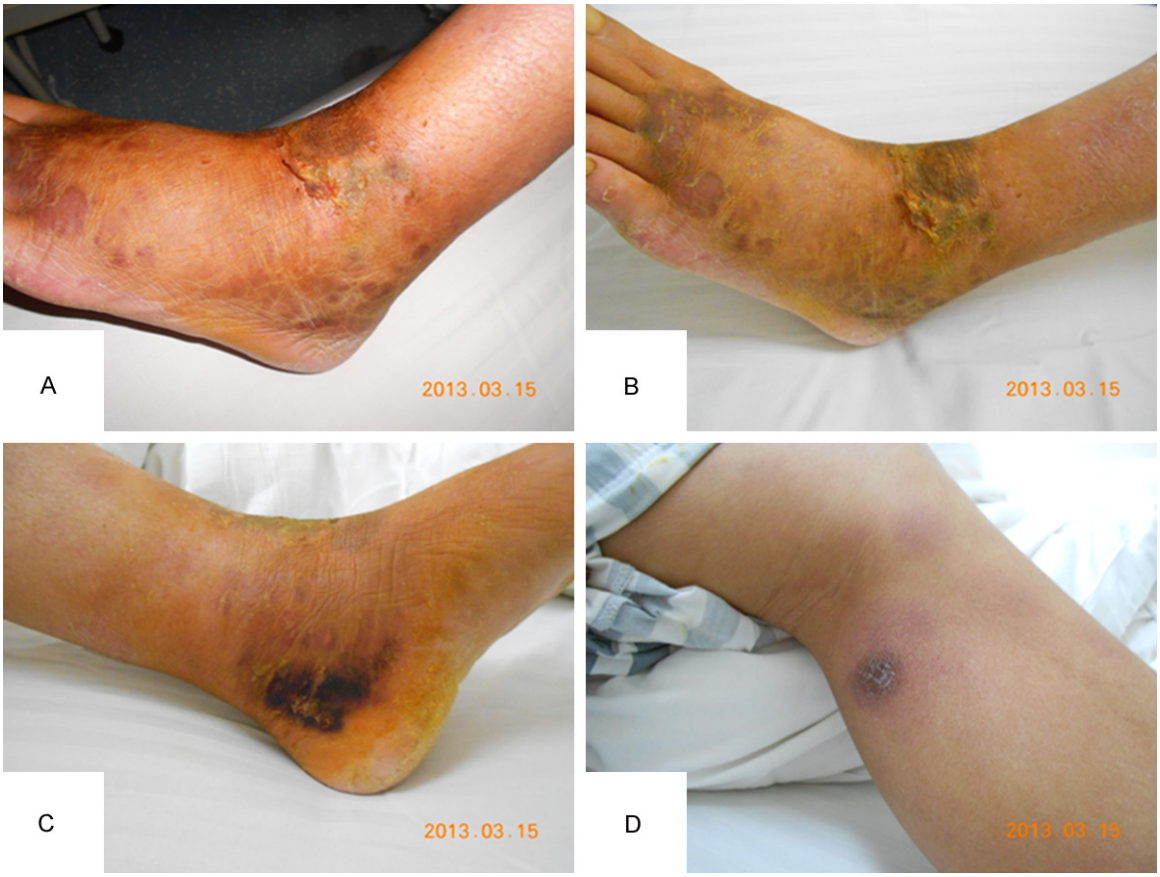

Figure 1. A-C showed that there was localized ulceration with peripheral blackish-brown pigmentation on the left foot, which was slightly swelling; D: A subcutaneous nodule with blackish-brown pigmentation, accompanying two peripheral erythematous patchs on the right calf (These pictures were taken after the first-period chemotherapy).

However, little effect appeared after applying hormone and immunosuppressant. 4 days before visiting our hospital, a subcutaneous nodule with normal skin temperature presented in his left calf, and then spread rapidly to lower limbs, upper extremities, trunk, neck and occiput in 10 days. But the patient reported no systemic positive symptoms such as fever, chills, night sweats and weight loss. He was otherwise healthy with no other relevant history. Lymphadenopathy and hepatosplenomegaly were absent. Both routine blood test and bone marrow examination were normal. Laboratory data showed increased ESR. As far as subcutaneous nodule was concerned, at the moment the most likely differential diagnosis included panniculitis and sarcoidosis. Meanwhile, tumor such as lymphoma had to be taken into consideration. In order to clarify the diagnosis, a biopsy of subcutaneous nodule for pathology had been done.

Microscopically, H&E staining sections showed a diffuse subcutaneous lymphocytic infiltration with tumor necrosis and angiovation, involving epidermis or not. The rim formed by neoplastic T lymphocytes around the individual fat cells in the subcutaneous lobules could be seen. Tumor necrosis was extensive (**Figure 2**). CGD-TCL had immunophenotype of CD3+/CD4-/CD8-/βF1-with strong positive expression of CD56. And, the case had high positive expression of cytotoxic protein TIA-1. Proliferative marker, KI-67 showed distinctive nuclear reaction involving 80% neoplastic cells (**Figure 3**). In situ hybridization for EBV (EBER) was negative staining. Monoclonal rearrangement of TCRγ genes was identified by PCR-based analysis of TCRγ genes rearrangement using the biopsy specimen. So we made the diagnosis of primary cutaneous γδ-T-cell lymphoma (CGD-TCL).

The patient was treated with chemotherapeutic regimens-CHOP (cyclophosphamide, doxorubi-

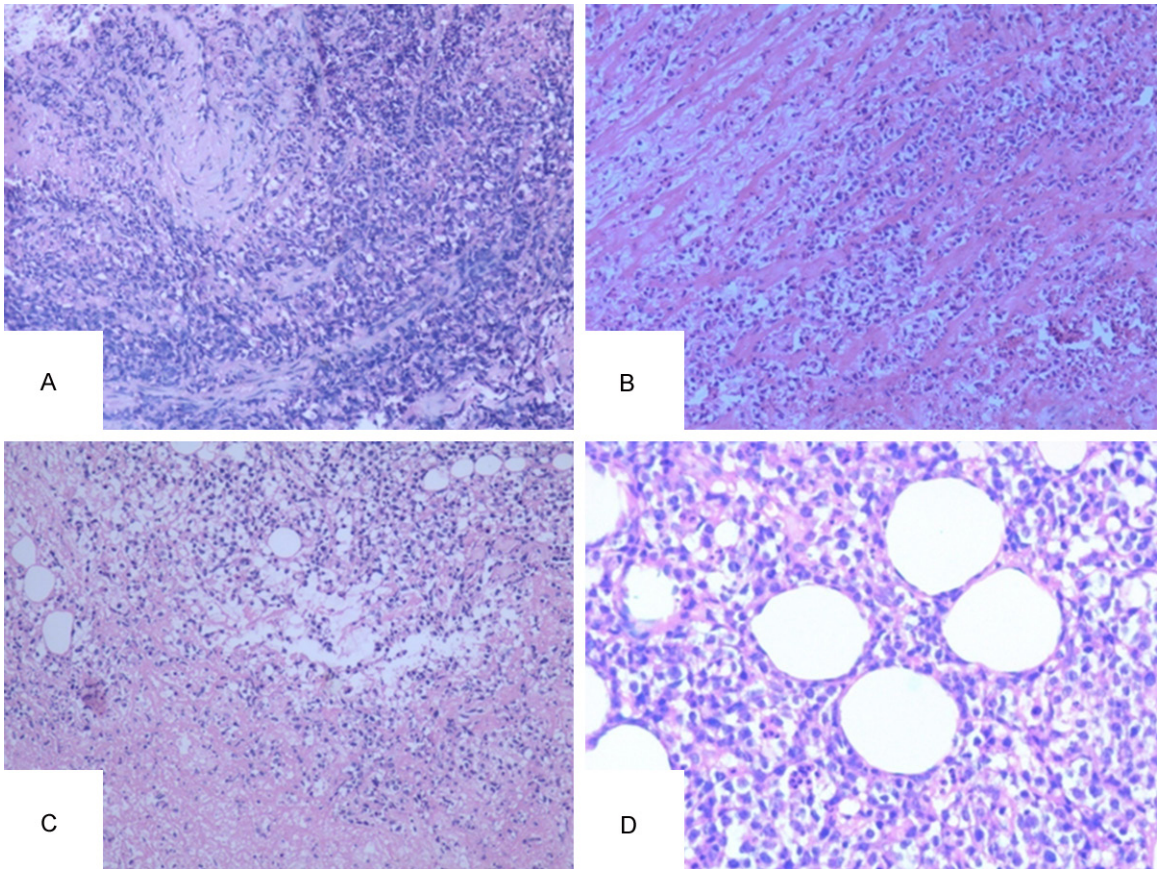

Figure 2. A: Focal angioinvasion; B: Pleomorphic, atypical T lymphocytes distributed between collagen bundles; C: Tumor necrosis (H&E, ×100); D: The "rimming" of fat cells by neoplastic cells in the subcutaneous fat (H&E, ×200).

cin, vincristine and prednisolone). After one period of chemotherapy, subcutaneous nodules became small, even disappeared, swelling and ulcer in the left pedal gone away gradually. What finally left was local blackish-brown pigmentation. Unluckily, one month later after first chemotherapy, tumor relapsed with lesions growing back rapidly, and computed tomography scan of chest showed scattered pleomorphic high density shadows in patient's double lungs (**Figure 4**). The patient refused lung biopsy and he was just 10-month survival time from the onset. The patient ultimately died of infection and multiple organ failure.

Discussion

CGD-TCL presents a wide range of clinical manifestations. Its lesions which commonly distribute in the extremities and trunk can be characterized by patches, plaques, nodules, necrotic tumors and often accompanied by the ulceration. However, systemic symptoms such as fever, hepatosplenomegaly and hemophagocytic syndrome are rare. For the most important, misdiagnosis is not uncommon because of the similar clinical characteristics with some autoimmune diseases such as nodular panniculitis, lupus erythematosus profundus, systemic vasculitis, erythema nodosum and so on [2]. So, during the diagnostic process, the emergence of above these clinical features should be considered to have the possibility of CGD-TCL.

Microscopically, H&E staining sections show a diffuse subcutaneous lymphocytic infiltration with tumor necrosis and angioinvation, involving epidermis or not. The rim formed by neoplastic T lymphocytes around the individual fat cells in the subcutaneous lobules can be seen. Apoptosis and necrosis are common and sometimes extensive. CGD-TCL has immunophenotype of CD3+/CD4-/CD8-/βF1- with co-expression of CD56 frequently. And, almost all cases have strong expression of cytotoxic proteins

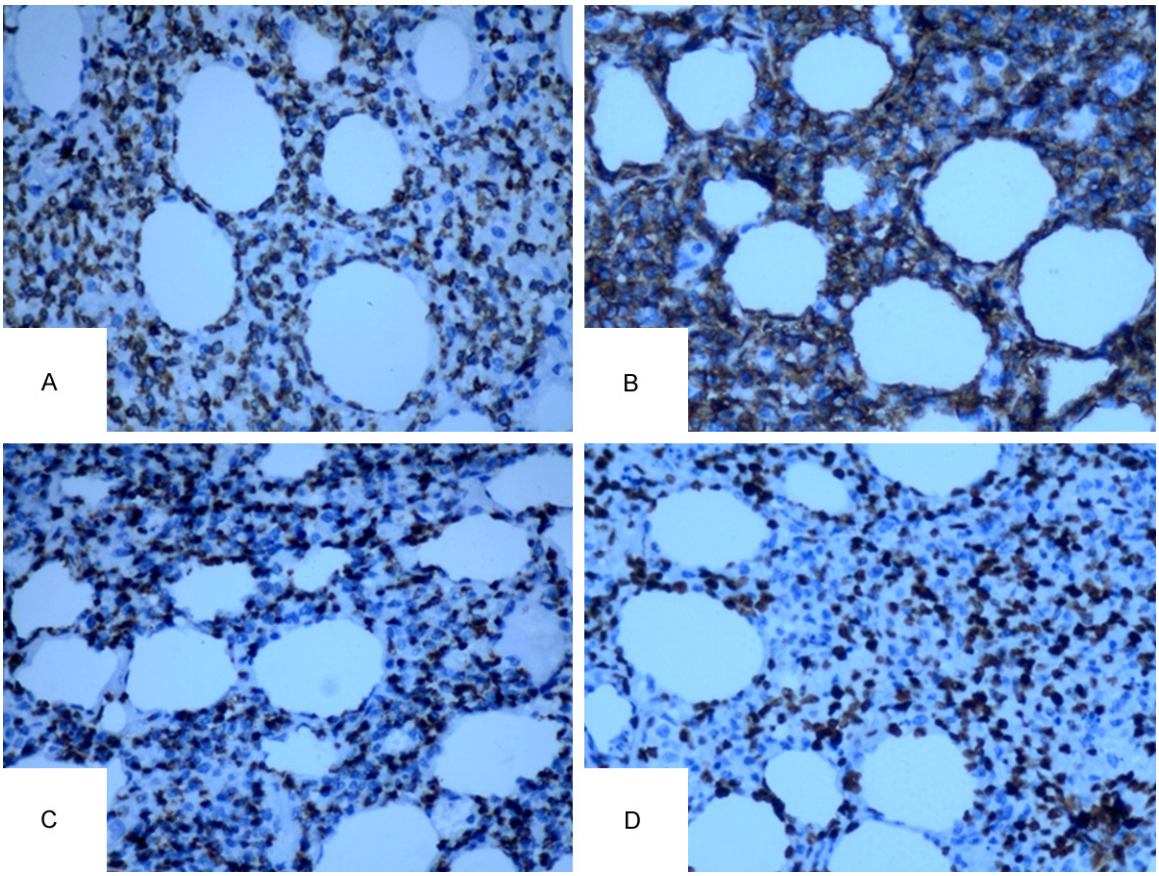

Figure 3. A: Tumor cells were positive for CD3; B: Strong expression of CD56; C: Tumor cells were positive for TIA-1; D: High proliferative activity of Ki-67. (IHC, DAB staining, ×200).

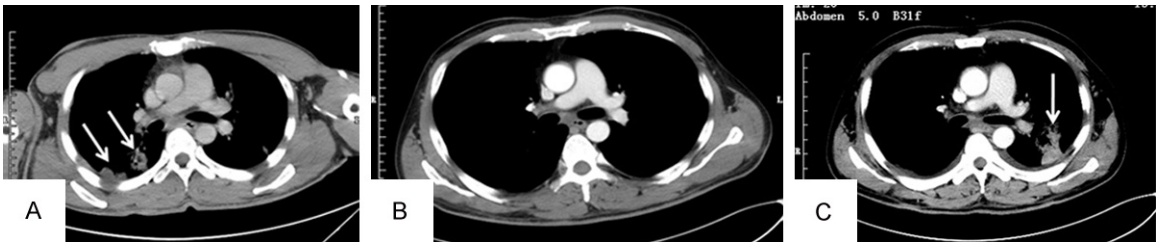

Figure 4. CT showed metastases (white arrows) in the lungs. A: Before the chemotherapy; B: After two courses of chemotherapy; C: Nearly three months after the chemotherapy.

(granzyme B, TIA-1, perforin). Ki-67, which presents proliferative activity of tumor cells, is also strong positive staining. In situ hybridization for EBV (EBER) is usually negative. In addition, monoclonal rearrangement of TCRγ genes can be detected.

So far, there is not recognized standard treatment for CGD-TCL. Although single-agent or systemic multi-agent chemotherapy combined with radiation therapy or not are main therapies strategies nowadays. However, patients with PCGD-TCL are usually likely to have chemoresistance and radioresistance. In recent de cades, immunomodulatory therapy such as cyclosporin A and denileukin diftitox is also a kind of choice, it was reported that weekly infusions of denileukin diftitox after local radiotherapy could result in complete remission of CGD-TCL [3]. Some other study reports that allogenic stem cell transplantation may be another therapy strategy, Sarah et al reported one case of CGD-TCL with remission after allogeneic stem cell transplantation [4, 5]. Moreover, there are

some reports about the treatment of CGD-TCL with retinoid [6] or narrow band UVB [7], but which effects need further verification. CGD-TCL is a highly aggressive tumor with a 15-month median survival [8]. However, not all patients with γ/δ T-cell lymphomas carry out poor prognosis. In 5 cases of CGD-TCL reported by Magro et al., two patients had lived for 5 years after diagnosis, and other three patients had been complete remission after intervention [9]. Furthermore, it was illuminated that hemophagocytic syndrome [10] and low white blood cell count could be identified as independent factors associated with poor prognosis.

All in all, primary cutaneous γ/δ T-cell lymphoma is a highly complicated and heterogeneous tumor with various clinical manifestations and easy to be misdiagnosed at the beginning. In the present reported case, the patient first showed swelling and pain in left foot firstly, followed by ulceration in left ankle. Subcutaneous nodule did not arise until 5 months later, and then spread crazily and rapidly over the body. Pedal swelling and ulceration which had failed to respond to previous treatment, obtained great improvement as soon as applying chemotherapy. From our perspective, foot lesions are primary focus to consider CGD-TCL, and ulceration is the result of the disease involving the epidermis. The blocking of blood flow may be the pathological basis of swelling, which was caused by destruction of blood vessels and lymph-vessel by neoplastic cells invasion.

Although almost all patients present with nodular or plaque-like lesions simulating a panniculitis [11], subcutaneous nodule is not always presented in the primary symptom of CGD-TCL. As to early diagnosis and treatment, it is critical to keep vigilant about other first symptoms such as swelling, especially when ulceration appears. It is of great significance to improve the prognosis of patient with CGD-TCL through making early diagnosis and providing sufficiently appropriate treatment.

In summary, we reported a case of CGD-TCL with unilateral lower extremity swelling. To our knowledge, this case is the first report of CGD-TCL with unilateral lower extremity swelling as the first-onset symptom. If patient is presented the first symptoms such as swelling of extremities, especially when ulceration appears, it is of great significance to be considerate about the possibility of CGD-TCL.

Disclosure of conflict of interest

None.

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