Primary extranodal head and neck classical Hodgkin lymphoma: A rare clinical case report

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Abstract. The subcutaneous soft tissue of the forehead is a rare anatomic site for Hodgkin lymphoma (HL), and no such case has previously been reported in the literature, to the best of our knowledge. HLs commonly present in the nodal regions in the majority of patients, rarely occurring in extranodal sites, whereas primary extranodal lymphoma is less common and is more typical in cases of non-HL. The present study reports a novel case of extranodal head and neck classical HL (cHL), initially diagnosed as frontal fibroma. The present study describes an unusual case of subcutaneous soft tissue involvement of HL, aiming to enhance current levels of awareness for patients with extranodal symptoms. A 25-year-old male, who inadvertently detected a hard painless mass above the right superciliary arch 2 months prior to admission in April 2013 was eventually diagnosed with mixed cellularity cHL. Subsequent to six cycles of doxorubicin (Adriamycin), bleomycin, vindesine and dacarbazine chemotherapy, followed by four cycles of ifosfamide, gemcitabine, vinorelbine and prednisone chemotherapy, a satisfactory curative effect was obtained. In conclusion, it is proposed that lymphoma should be considered in the differential diagnosis of a mass involving the subcutaneous soft tissue.

Introduction

Hodgkin lymphoma (HL) is a malignant neoplasm of the lymphatic tissue and one of the few adult malignancies that can be successfully treated in the majority of cases (1). It is commonly found in the lymph nodes, spleen, liver, bone marrow and other sites, with an incidence of 2-4 per 100,000 individuals annually (2). HLs predominantly involve the lymph nodes and only ~5% arise in extranodal sites, in contrast to 30% of non-HL cases presenting in extranodal sites (3). Primary extranodal lymphoma is less common and is predominately non-HL (4-7).

Approximately 5% of all malignant neoplasms of the head and neck are malignant lymphomas, which may include the involvement of nodal or extranodal sites (8). The head and neck region is the second most common anatomical site of extranodal lymphomas. In HL, the development and spreading of extranodal lesions may occur in any organ system, simulating other infectious or neoplastic diseases (9). Extranodal involvement constitutes an important pretreatment prognostic factor in patients with lymphoma, and its incidence has increased in the last two decades (10). Numerous studies have indicated that extranodal disease involving >1 site presents a worse outcome (11).

In non-HL, the second most common site of extranodal involvement is the skin, with the gastrointestinal tract being the first most common site (12). Unlike non-HL, in which skin involvement is well-recognized, skin infiltration of HL is extremely rare and is associated with poor prognosis. The frequency of skin involvement is estimated to be 3.4% in HL, and its most common clinical presentation is a single or multiple dermal or subcutaneous nodules (13).

Despite recent scientific progress, pathological (immunohistochemical and morphological) examination is highly beneficial in the diagnosis of HL (14). Morphologically, classical HL (cHL) is characterized by neoplastic multinucleated mononuclear Hodgkin and Reed-Sternberg (RS) cells, which typically account for 1-5% of all cells in a cHL specimen (15). These cells were associated with a microenvironment that consists of abundant non-neoplastic cells, such as plasma cells, granulocytes, histiocytes and lymphocytes, in varying proportions (16).

cHL has a bimodal age incidence, with the majority of cases occurring between the ages of 15 and 35 years, and a second peak incidence observed in older adults (11). No clearly defined risk factors have been identified for the development of HL, and the cause of the disease has yet to be elucidated. Certain factors demonstrated to be associated with HL include immune suppression, viral exposures and familial factors (12). Patients with extranodal involvement were predominantly young males, and the majority of the patients exhibited stage IV disease (13).

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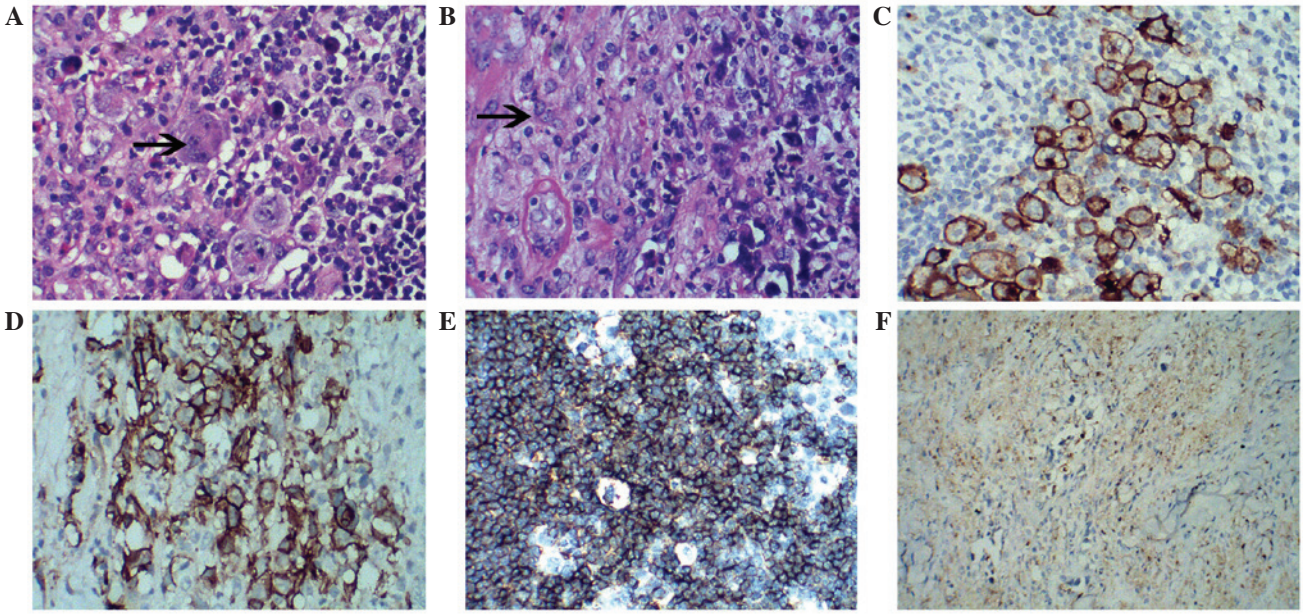

Figure 1. Pathological and immunohistochemical staining of the forehead and cervical lymph node masses. (A) Hematoxylin-eosin (HE) staining of the left cervical lymph node indicated the presence of scattered Reed-Sternberg cells (arrows), which are characteristic of Hodgkin lymphoma, and numerous lymphocytes and eosinophils (magnification, x400). (B) Right frontal neoplasm HE staining indicated scattered Reed-Sternberg cells (magnification, x400). CD30 immunohistochemical staining of the (C) cervical lymph node mass and (D) right frontal neoplasm revealed large neoplastic cells, which were stained brown (HE counterstain; magnification, x400). (E) Immunohistochemical staining of the lymph node tissue for CD20 demonstrated local strong lymphoid aggregation (magnification, x400). (F) Negative immunohistochemical staining of the right frontal neoplasm for KP1 (magnification, x200).

In the present case, a 25-year-old male, who presented with a hard painless mass above the right superciliary arch 2 months prior to admission, was subsequently diagnosed with mixed cellularity cHL. To the best of our knowledge, this is the first report of such a case. Written informed consent was obtained from the patient.

Case report

A 25-year-old male, with a 2-month history of a painless right frontal neoplasm with a similar hardness to that of a bone fibroma, presented at the Department of Otolaryngology Head and Neck Surgery (Shanghai First People's Hospital, Shanghai, China) in April 2013 for diagnosis and surgical treatment. Soon after the presentation of the first mass, the patient detected another mass on the sternum, which had similar characteristics to the initial mass. After ~1 month, the patient identified a 1x2-cm sized mass in the left cervical lymph node, without pain or fever. Prior to admission at the Shanghai First People's Hospital, a head computed tomography (CT) scan had been performed at a different hospital, and the imaging diagnosis indicated frontal fibroma; however, the patient refused treatment and was subsequently admitted to our hospital. In addition to the aforementioned symptoms, the patient did not experience any discomfort, and his daily life had not been affected significantly.

The involvement of forehead and cervical lymph node rendered the presence of an otolaryngologist necessary to participate in the detection and identification of the lesion. Through a series of preoperative blood tests, the patient was diagnosed with hepatitis B. Subsequent to the relevant examinations, the patient underwent surgery performed at the Department of Otolaryngology Head and Neck Surgery as his symptoms were consistent with frontal fibroma. During surgery, the hard mass on the right frontal area was found to be part of the subcutaneous soft tissue, in proximity to the frontal bone surface but with a relatively clear boundary. Therefore, the enlargement on the left cervical lymph node was removed, in addition to the frontal neoplasm, and both were subjected to pathological analysis. As the surgery was performed by the Department of Otolaryngology Head and Neck Surgery, the sternum mass was not removed.

Postoperative pathology results were pathologically atypical. Subsequent to a discussion of the case with clinicians from Shanghai Ruijin Hospital and Zhongshan Hospital, a repeat immunohistochemical staining was performed and the patient was diagnosed with cHL of mixed cellularity with right frontal soft tissue involvement. Samples from the patient were fixed in buffered formalin, paraffin embedded and cut into 4-mm-thick sections prior to staining with hematoxylin-eosin (HE). Histological analysis with HE staining was performed on the mass of the left cervical lymph nodes (Fig. 1A) and the right frontal subcutaneous soft tissue (Fig. 1B). Immunohistochemical staining was conducted on fixed, paraffin-embedded tissue sections using mouse anti-human CD30 (1:50; IS602), CD20 (1:200; IS604) and KP1 monoclonal antibodies (1:4,000; IS609; all Dako North America, Inc., Carpinteria, CA, USA). The results of immunohistochemical staining revealed that the lymph node mass (Fig. 1C) and the forehead subcutaneous soft tissue (Fig. 1D) were CD30-positive. In addition, the lymph node tissue was also CD20-positive (Fig. 1E), and the right frontal subcutaneous soft tissue was KP1-negative (Fig. 1F). As some studies on cHL cases have demonstrated that RS-H cells have a typical immunophenotypic profile: $CD15^+$, $CD30^+$, while high $CD20^+$, dispersed cells exhibited a significant correlation with longer overall survival and a trend toward improved

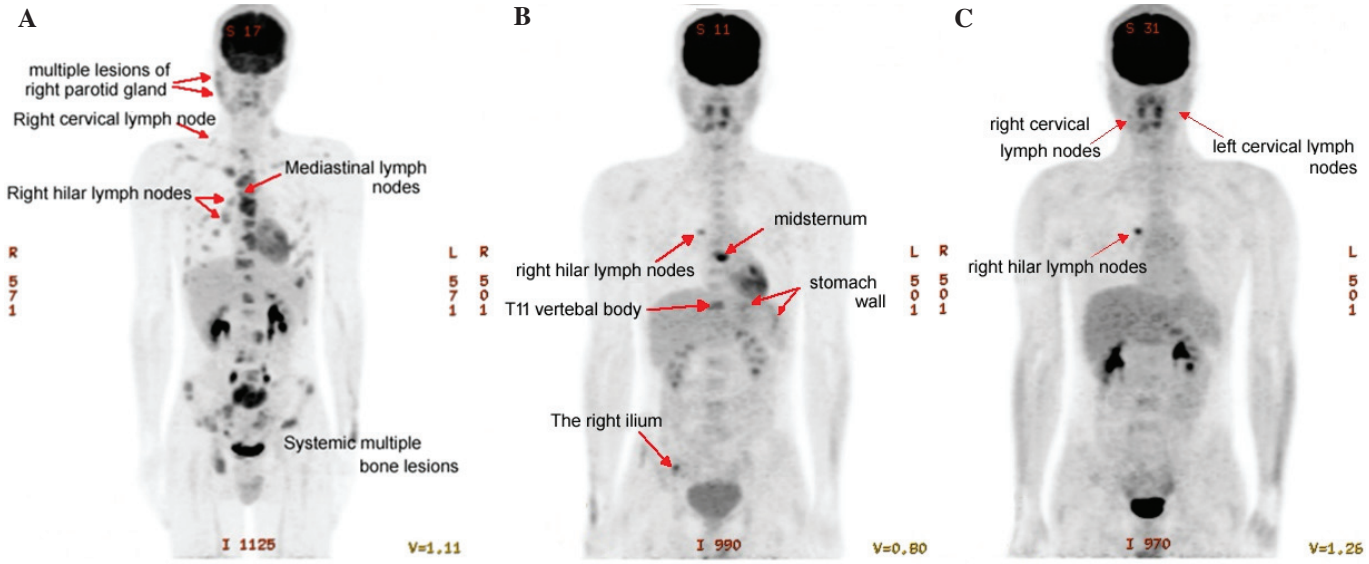

Figure 2. PET-CT scanning image manifestations. (A) PET-CT scan performed prior to ABVD chemotherapy. Multiple lymph node masses were observed on the right of the neck, right supraclavicular, right hilar and mediastinal sites, as well as systemic multiple bone lesions. (B) PET-CT scan performed following eight cycles of ABVD chemotherapy. (C) PET-CT scan performed following six cycles of IGEV chemotherapy. PET-CT, positron emission tomography-computed tomography; ABVD, doxorubicin (Adriamycin), bleomycin, vindesine and dacarbazine; IGEV, ifosfamide, gemcitabine, vinorelbine and prednisone.

progression-free survival (17,18). Kamper *et al* (18) showed that high expression of CD68 (KP1) and CD163 in cHL cases correlated with the presence of RS-H cells infected by EBV. Based on the aforementioned findings, the patient was transferred to the Department of Hematology for treatment. The progression of disease and the effectiveness of the treatment was monitored by the present authors. During the treatment, a biopsy of the sternum nodule was performed, which was not found to be relevant to the disease.

During the treatment course at the Department of Hematology, the patient received positron emission tomography (PET)-CT examination. The results indicated that the right cervical, right supraclavicular, right hilar and mediastinal sites presented multiple lymph node masses and systemic multiple bone lesions (Fig. 2A). According to the Cotswold staging system (19), the patient was classified as stage IV B with soft tissue and bone involvement. The patient was treated with six cycles of conventional and two cycles of consolidation chemotherapy according to the doxorubicin (Adriamycin), bleomycin, vindesine and dacarbazine (ABVD) regimens, and obtained a satisfactory curative effect. A total of 400 mg Adriamycin, 15 mg Bleomycin, 4 mg Vindesine and 600 mg Dacarbazine was administered at day 1, followed by a 15-day interval prior to the same treatment, which composed a complete chemotherapy cycle. A one-month break was included between each chemotherapy cycle. A second PET-CT was performed in March 2014 following the eight cycles of chemotherapy (Fig. 2B), and the results indicated that the right hilar lymph node mass had increased in size, while multiple bone lesions remained on the gladiolus, T11 vertebral body and the right ilium. Compared with the initial PET-CT scan, the tumors were significantly decreased, but several lesions remained. Therefore, the hematologist at our hospital administered a further six cycles of ifosfamide, gemcitabine, vinorelbine and prednisone (IGEV regimen), and the patient exhibited a significant improvement. The IGEV regimen included 1.4 g gemcitabine and 30 mg vinorelbine at day 1, and 2 g ifosfamide and 100 mg prednisone at days 1-4. Following the aforementioned therapy, a third PET-CT scan was performed with a full-body PET scanner in 3-dimensional mode (Fig. 2C). The scan revealed multiple tumors invading the sternum, thoracic vertebra, ribs and ilium. Compared with the former PET-CT scan (Fig. 2B), the glucose metabolism of the bone lesions had recovered to a normal level, as it was no longer aggregated, which indicated that the treatments were effective in achieving a partial response.

Discussion

The World Health Organization 2008 classification recognizes two histological subtypes of HL, including the nodular lymphocyte-predominant and the cHL subtypes. cHL includes the following four entities: Nodular sclerosis, mixed cellularity, lymphocyte-depleted and lymphocyte-rich cHL (20). The majority of HL patients present with asymptomatic superficial lymphadenopathy. The predominant sites of disease include the supraclavicular, mediastinal and cervical lymph nodes, while hepatic or bone marrow involvement and subdiaphragmatic presentation are less common (3,15). In addition, extranodal presentations are considerably rare (1). Typically, HL presents with lymph node involvement. Primary extranodal lymphoma is not commonly observed, and the majority of such cases present non-HL disease (5).

In the present case, the patient initially discovered a frontal subcutaneous nodule. This was followed by the detection of a further nodule on the sternum, which demonstrated similar characteristics to the former lesion. After ~1 month, the patient noticed a mass of reasonable hardness on the left side of the cervical spine. Following case discussion and repeated immunohistochemical staining, the postoperative pathological findings eventually resulted in a diagnosis of mixed cellularity type cHL, involving the frontal subcutaneous

soft tissue. Thus, the current case cannot be considered as a primary skin lymphoma. The most common skin involvement in lymphoma is adult T-cell lymphoma, which is also associated with widespread lymphadenopathy, bone marrow and blood involvement (21). Skin involvement in HL is rare and also associated with poor prognosis (22).

In mixed cellularity cHL, diffuse or vaguely nodular infiltrate is observed, without band-forming sclerosis, although fine interstitial fibrosis may be present. RS cells are more typically detected in cHL, rather than in nodular sclerosis. Mixed cellularity cHL presents predominately in adults and male patients, and the stage upon diagnosis is frequently more advanced than in nodular sclerosis or lymphocyte-predominant disease, with involvement of lymph nodes, spleen, liver or bone marrow (1).

Primary lymphoma of the bone is rare, comprising ~5% of all primary bone malignancies and ~5% of extranodal lymphomas (16). Fluorodeoxyglucose-PET scanning has emerged as an important tool in the staging of patients with HL by significantly enhancing the staging information obtained using other standard radiographic methods, such as X-ray and CT (23). In the current study, the patient was clinically diagnosed with stage IV disease, thus the primary source of the lymphoma cannot be determined; however, it is evident that the tumor involved the bones.

All types of cHL typically receive similar treatment (20), based on the disease stage. PET-CT has an important role in diagnosis and the evaluation of the effects of chemotherapy (24). A series of randomized trials in the past decades have established ABVD as the gold standard on the basis of its efficacy and ability to reduce the associated long-term toxic effects (25,26). ABVD is also the standard chemotherapy treatment for patients with advanced-stage disease (1). By December 2013, the present patient had completed six cycles of ABVD chemotherapy and two cycles of consolidation chemotherapy. The patient exhibited a partial response to chemotherapy, with no evident adverse effects. Following admission to the Shanghai First People's Hospital, the patient underwent treatment with two different chemotherapy regimes (ABVD and IGEV). At present, the patient's general condition is stable and after accepting an autologous bone marrow stem cell transplant in May 2014, the patient received immunosuppressive therapy and attended outpatient follow-ups every month. At the most recent follow-up in May 2016, the patient was stable and did not report any discomfort. Clinical follow-up will be continued.

In conclusion, extranodal cHL of the head and neck is rare, while cHL with subcutaneous soft tissue involvement is even rarer. In particular, primary HL of the skin is so rare that several features have yet to be elucidated. Detailed physical examination and medical history collection is necessary, and HL should be considered in patient's with enlarged painless cervical lymph nodes. Therefore, clinicians should pay attention to clinical symptoms similar to bone fibroadenoma and share similar cases in order to provide better diagnosis and treatment for cases of HL with skin involvement.

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