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Case Report

Pediatric anaplastic large cell lymphoma misdiagnosed as multiple organ abscesses: a case report and literature review

Wenmin Yang[1], Yunlong Zuo[1], Yiyu Yang[1], Jianping Tao[1], Jie Hong[1], Zhiyuan Wu[1], Feiyan Chen[1], Run Dang[1], Yufeng Liang[1], Yang Li[2], Dabo Liu[1]

[1]Guangzhou Women and Children's Medical Center, Guangzhou 510115, Guangdong, China; [2]The First Affiliated Hospital of Zhongshan University, Guangzhou 510115, Guangdong, China

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Abstract: We report the case of a 6-year-old male with fever, left maxillofacial swelling, cervical and mediastinal masses, and lymphadenopathy who developed respiratory failure and shock caused by tracheal compression and superior vena cava reflux disorder. The initial diagnosis was maxillary sinus, cervical, and mediastinal abscesses. Initial treatments included maxillary sinus abscess resection, neck abscess incision drainage, and antibiotics. Anaplastic large cell lymphoma (ALCL) was diagnosed ultimately according to pathological and immunohistochemical examination of cervical lesion biopsy tissue. We analyze the reasons for misdiagnosis by comparing clinical and pathological features of ALCL to other systemic illnesses that cause lymphadenopathy.

Keywords: Anaplastic large cell lymphoma, child, misdiagnose, abscess, differential diagnosis

Introduction

Anaplastic large cell lymphoma (ALCL) is a rare systemic, large-cell, malignant non-Hodgkin lymphoma (NHL) characterized by expansion of cells with pleomorphic appearance expressing the CD30 antigen [1]. The rate of misdiagnosis is high due to the variety of nonspecific clinical manifestations. To raise awareness of potential misdiagnosis, we report a pediatric ALCL case initially diagnosed with multiple organ abscesses. The child was ultimately diagnosed with ALCL according to pathological and immunohistochemical examination and responded well to BFM-95 regimen chemotherapy.

Case report

A 6-year-old male was admitted to our hospital on January 6, 2015 with neck swelling for more than half a month. One month earlier, he had received left maxillary sinus abscess removal surgery.

On October 18, 2014, he was taken to a dental outpatient hospital because the left upper back gingiva and left nasal eye had been swollen for ~2 weeks. Radiography showed widening of the periodontal ligament space and separation of the associated teeth and medullary cavity (**Figure 1**). He was diagnosed with periapical periodontitis. The gingival tumefaction was relieved after pulp exposure, pulp extirpation, rinsing, and incision and drainage, but the left face remained swollen. He was admitted to another hospital on November 20, 2014 with swelling of the left jaw of one months' duration and fever for 10 days. Head-neck-chest CT scan showed (1) thickening of the left maxillary sinus mucosal layer and local bone destruction and (2) multiple lymph node enlargement in the left mandible, neck, and infraclavicular regions, and in the mediastinum (**Figure 2**). Diagnoses were left maxillary sinus and jaw abscess, left maxillary sinus cyst, and cervical lymphadenitis. Left maxillary sinus inflammation was partially alleviated following maxillary sinus abscess resection and postoperative anti-infection treatments. On December 20, 2014, the left neck lymph nodes were again swollen. While this subsided after a few days, a soybean-sized mass appeared on the right front side of the

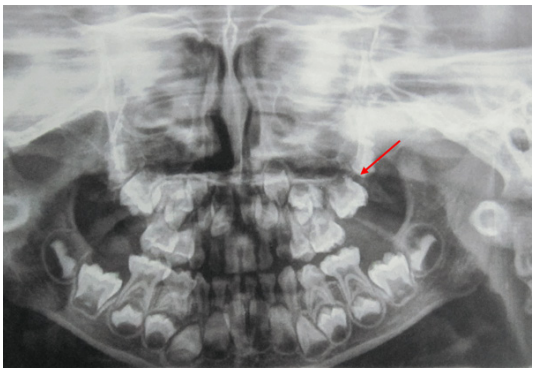

Figure 1. X-ray showing widening of periodontal ligament space and separation of the associated teeth.

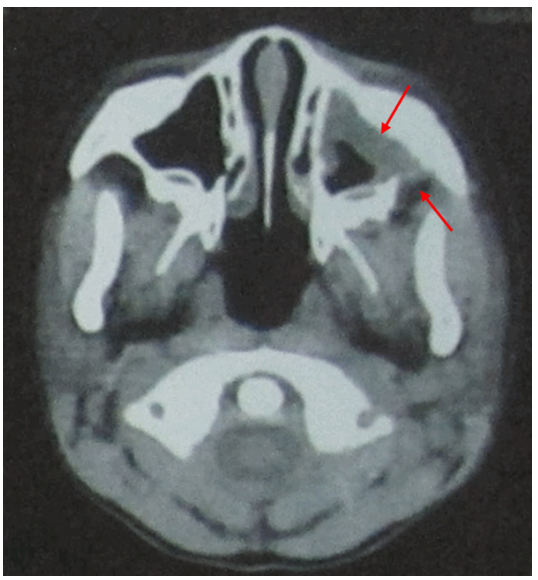

Figure 2. CT showing local bone destruction in the maxillary sinus.

neck that swelled progressively until it reached the right back of the neck. The child also exhibited fever, night sweats, and body weight loss. He was admitted to the surgical department of our hospital by the emergency department with a preliminary diagnosis of anterior cervical abscess.

Physical examination on admission: The subcutaneous mass could be felt from the right anterior neck to the mastoid, covering a region of about 2 × 8 cm. It was hard and associated with tenderness and high skin temperature, but there was no skin redness. It had no clear boundary and could not be moved. A few swollen lymph nodes could also be felt in the bilateral mandibular and groin regions, which ranged from soybean- to peanut-sized. The liver was also swollen and reached 3 cm below the ribs, but the spleen was of normal size and there were no other detectable masses. Cardiopulmonary physical examination revealed no abnormalities.

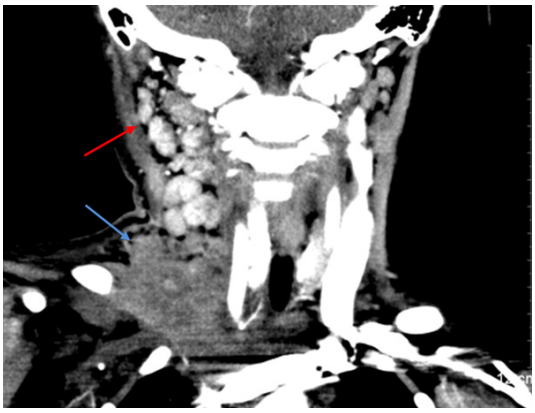

Figure 3. CT showing large mass lesions from the right supraclavicular fossa to the anterior region of the neck (blue arrow) and multiple lymph node enlargement of the right neck (red arrow).

Admission diagnosis: cervical lymphadenitis and abscess

Diagnosis and treatment: On 2015-01-07, CT revealed (1) masses from the right supraclavicular fossa to the anterior region of the neck, extending downward to involve the anterior superior mediastinum, (2) multiple lymph node enlargement on the right side of the neck, and (3) slight low-density shadow of the thyroid left lobe (**Figure 3**). Three B ultrasound examinations on 2015-01-03, 2015-01-06, and 2015-01-20 showed formation of an anterior cervical abscess. On 2015-01-07, we performed neck abscess incision and drainage followed by postoperative cefuroxime administration. However, right neck swelling increased gradually and extended to the chest area. On 2015-01-16, CT results indicated that the masses of the anterior portion and right supraclavicular fossa were larger than before, extending downward to involve both anterior and middle mediastinum and upward to the retropharyngeal space. In addition, CT also revealed multiple lymph node enlargement on the right side of the neck, pericardial effusion, bilateral pleural effusion, and superior vena cava compression. On 2015-01-19, his neck and chest wall were markedly swollen and he showed symptoms of dyspnea.

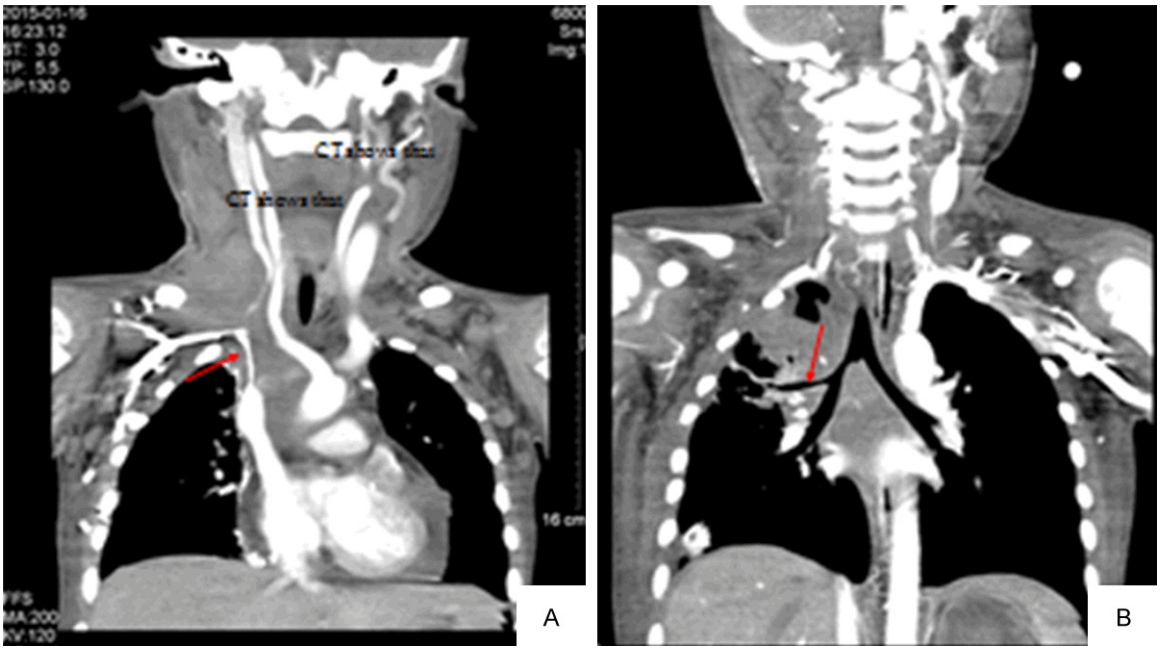

Figure 4. A. CT showing multiple lymph node swelling in the right neck and mediastinum, and compression of the superior vena cava. B. CT showing compression of the right main bronchus.

Oxygen saturation was 80%~90%, and he was transferred to ICU.

Physical examination at transfer: The neck and chest wall were swollen, local skin temperature was high, bilateral lung breath sounds were weak with wheezing, and heart sounds were low and distant. On 2015-01-20, cardiac color sonography showed moderate pericardial effusion. On 2015-01-20, tracheal intubation and mechanical ventilation were started due to unstable oxyhemoglobin saturation. After consultation with thoracic surgeons, he was tentatively diagnosed with retropharyngeal and mediastinal abscess, right pleural effusion, and pericardial effusion. On 2015-01-20, mediastinal mass biopsy and fenestration of the pericardium were conducted. The mediastinal mass was hard and hemorrhaged after surgical separation. The right hilum dorsal tissue was sent for pathological examination. Pathological sections showed elevated lymphocytes and plasma cell infiltration, but no clear tumor. The pathological diagnosis was chronic nonspecific inflammation of fibrous connective tissue of the longitudinal diaphragm. The same pathological sections examined at another hospital showed numerous lymphocytes and histocyte-like cells, and the pathological diagnosis was mediastinitis and lymphnoditis. Considering the possibility of infection, the patient received various anti-infection treatments in succession, including ceftazidime, bangladesh ester, cefepime hydrochloride sodium, sodium fusidate, metronidazole, sulperazon, and vancomycin, anti-inflammatory therapy with dexamethasone, replacement treatment with thyroxine, and supportive treatment with albumin, globulin, and electrolytes.

Despite treatment, his face and chest wall edema gradually increased. Ventilator parameters, peak inspiratory pressure (PIP), CO_2 retention, airway obstruction, and superior vena cava pressure also increased gradually, and hypotension shock appeared repeatedly, with lowest blood pressure of 74/40 mmHg. Several neck and chest CT examinations revealed multiple lymph node swelling in the right neck and mediastinum and compression of the superior vena cava, right pulmonary artery, and right main bronchus (**Figure 4**). On 2015-01-21 and 2015-01-29, two fiber optic bronchoscopy examinations showed narrowing of the trachea and right bronchial stenosis due to compression. Fluid and vasoactive agents were used to treat shock. We performed closed thoracic drainage surgery due to pneumothorax. **Table 1** shows the ventilator parameters of peak pressure and tidal volume from 2015-01-24. We

Table 1. The parameters of peak pressure and tidal volume in mechanical ventilation

Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
PIP (cm H_2O)	20	20	18	20	20	20	35	35	31	38	53	50	45	35	30	40	43	55	38	26
VT (ml)	208	226	209	210	170	155	150	150	200	190	140	150	119	160	160	146	100	150	170	176

2015-01-24 was taken as the first day.

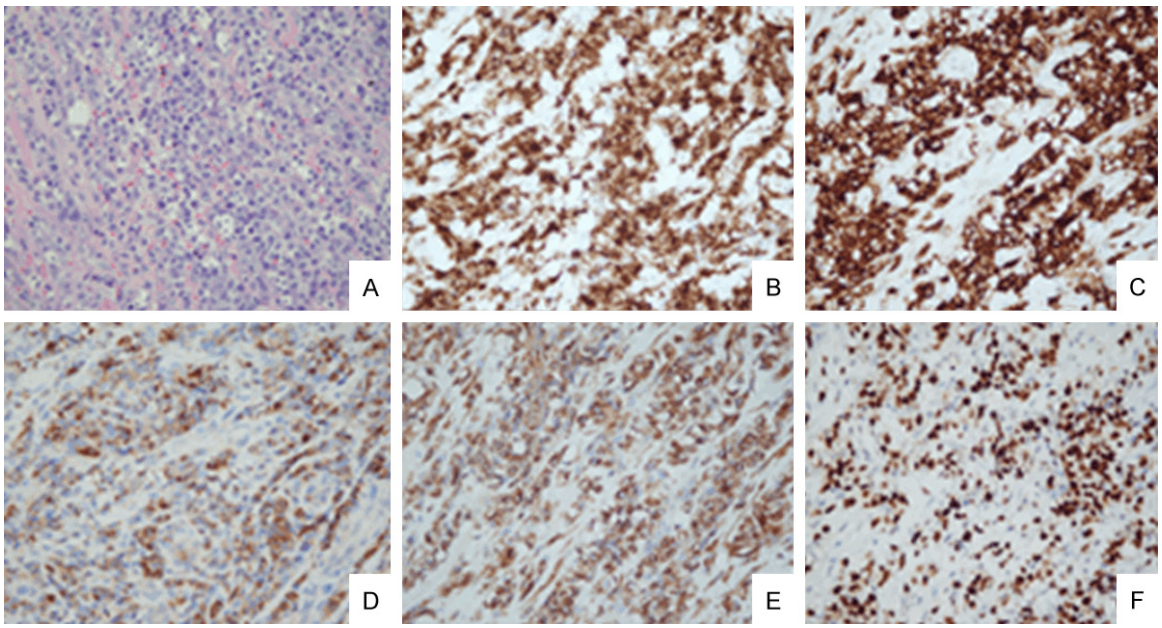

Figure 5. Hematoxylin and eosin (A) and immunohistochemical staining (B-F) of biopsy tissue under light microscopy (40 × 10 times). (A) Hematoxylin and eosin staining showing large round or reniform tumor cells with oval or reniform nuclei. (B-F) Immunostaining for (B) ALK, (C) CD30, (D) EMA, (E) vimentin, and (F) Ki-67.

performed a right cervical lesion biopsy on 2015-02-04. The hard subcutaneous tissue exposed during the operation was conglutinated to the sternocleidomastoid and adjacent lymph node, and both the sternocleidomastoid and lymph node were stiff. We resected most of the sternocleidomastoid and lymph node tissue and sent samples to both our hospital pathology department and that of another hospital for examination. On 2015-02-11, the pathology report of the other hospital indicated tumor cell infiltration in all tissues and focal necrosis of muscle tissue. The tumor cells were large and round or oval. Nuclei were oval or reniform with fine chromatin and occasionally visible nucleoli. Focal necrosis was visible and there were no intact lymph node structures (**Figure 5**). Immunohistochemical staining revealed tumor cells positive (+) for CD30, anaplastic lymphoma kinase (ALK), CD43, TIA-1, epithelial membrane antigen (EMA), vimentin, and CD99 (**Figure 5**). Some cells were UCHL-1(+) and/or BCL-6(+). About 90% were Ki-67(+). Cells were negative for CK, CD5, CD3, CD79a, CD20, CD56, CD34, MPO, CD10, TdT, Bcl-2, CD38, CD138, S-100, CD1a, CD31, myogenin, and MyoD1. The final pathological diagnosis, considering both cell morphology and immunohistochemistry, was ALK(+) ALCL. On 2015-02-16, our own pathology department confirmed these results.

Other test results: Ultrasound showed enlarged liver. PET-CT showed no brain lesions. Routine blood tests showed peak WBC of 21.1 × 10^9/L, neutrophil 80%, band neutrophil 4%, ALT 151 U/L, AST 122 U/L, and ALB 36.2 g/L, normal Cr and CK-MB, TBIL 69.6 mol/L, DBIL 59.8 mol/L, LDH 543 U/L, hs-CRP 108 mg/L, and normal procalcitonin. Fungal dextran was normal on repeated examinations. Sputum smears were negative for mycobacterium tuberculosis.

Routine cerebrospinal fluid (CSF) cell and biochemical examinations were normal, CSF tuberculosis smear was negative, and there were no immature cells in CSF sediment smear.

Bacterial cultures of anterior cervical abscess, pericardial effusion, and pleural effusion were negative. Six separate blood cultures for bacteria and fungi were negative. Bone marrow cultures for bacteria and fungi were all negative. Bone marrow cytological examination revealed obvious active hyperplasia of granulocytes, red line, and giant nuclear systems, while platelets were normal. No obviously abnormal cell groups were detected by bone marrow leukemia immune typing. Rheumatoid factor and anti-streptolysin O were normal. Twelve auto-antibody and 4 vasculitis-related tests were negative. Serum Epstein-Barr virus (EB) antibody tests were negative and no plasma EB viral DNA was detected. Thyroid function test values were FT3 2.33 pmol/L, FT4 10.12 pmol/L, and TSH 0.194 IU/mL. Serum tumor six carbohydrate antigen-125 level was 37.70 U/mL. Both tuberculosis T-spot and PPD skin tests were negative.

The child was treated with BFM-95 regimen chemotherapy. On 2015-2-13, the V+AA BFM-95 regimen was successfully completed. At this time, shortness of breath was relieved and the neck tumor narrowed. On 2015-2-17, he was weaned off mechanical ventilation. On 2015-3-10, he was treated with the BB course, on 2015-4-5 with the CC course, and on 2015-4-28 with the AA course of the BFM-95 regimen.

After leaving the ICU, the child was monitored for 3 months. After four cycles of chemotherapy, the patient exhibited no fever, maxillofacial and neck tumors, superficial lymph node enlargement, or liver enlargement. There were no respiratory or cardiopulmonary abnormities. Follow-up routine blood tests were normal and there was no bone marrow inhibition.

Discussion

Reasons for misdiagnosis and other differential diagnosis

Studies from both China and abroad have reported a high rate of ALCL misdiagnosis, as it is often mistaken for inflammation, multiple organ abscesses, tuberculosis, or peripheral G lymphoma [2]. Immunohistochemistry is critical for differential diagnosis. In our case, the patient had been misdiagnosed four times with inflammatory lesions and abscesses. The first misdiagnosis was periapical periodontitis, so he was treated by pulp exposure, pulp extirpation, rinse, incision, and drainage. The second time, he was misdiagnosed with left maxillary sinus and jaw abscess and treated by maxillary sinus abscess excision. The third time, he was misdiagnosed with right neck infection and abscess, and treated by neck abscess incision drainage and antibiotics. The fourth time, the patient was diagnosed with retropharyngeal abscess, mediastinal abscess, and pericardial effusion, and treated by mediastinal abscess excision/biopsy and pericardial fenestration. The reason for misdiagnosis were fever, the presence of local masses with tenderness, high white blood cell count, high neutrophil fraction (%), neutrophilic bands, and high CRP. Repeated neck ultrasonography and CT indicated high possibility of maxillofacial, cervical, and mediastinal abscesses. The predominant pathological manifestation in tissue samples from the first surgery was lymphocyte infiltration, which suggested chronic inflammation. ALCL is easily misdiagnosed as inflammatory disease by pathology because this particular tumor is dominated by large lymphoid cells and is often accompanied by infiltration of inflammatory cells [3]. At this early stage, it is often difficult to diagnose ALCL by light microscopic examination alone. Immunohistochemical examination is particularly important for reducing the misdiagnosis rate of malignant lymphoma. The cardinal features for identifying this kind of tumor are irregular-shaped nuclei and large CD30-positive cells. These features may be missed in small biopsy tissue samples. Alternatively, due to low ALCL incidence, many treating clinicians and pathologists may have limited knowledge of these features.

Differential diagnosis

Common bacterial and fungal infections: Numerous bacterial and fungal infections were eliminated by negative puncture fluid, blood, and bone marrow culture results. Moreover, the child's condition was not improved by numerous antibiotics. In fact, his condition deteriorated. Retrospective analysis supporting ALCL include new or exacerbated symptoms after each treatment (antibiotics, hormones, anti-inflammatories, surgery) and imaging findings of new infiltrative changes, consistent with tumor progression and metastasis. During biopsy of the mediastinal mass, there was hemorrhage after separation, consistent with the rich blood supply of tumor tissue.

Other infectious diseases: tuberculosis, AIDS, Epstein-Barr virus: Some of his symptoms, including fever, night sweats, weight loss, neck mediastinal lymph node enlargement, and hepatauxe, are consistent with tuberculosis infection. However, the PPD skin test was negative, no tuberculosis mycobacterium was found in the pleural effusion or sputum smear, lymph node biopsy showed no specific tuberculosis-related changes (such as tubercle and caseous necrosis), and the T-spot test was negative. Children with AIDS can also have fever and lymph node enlargement, but no HIV antibodies were detected. Finally, children with EB virus infection can exhibit fever and lymph node enlargement; however, serum EB antibody tests were negative, no EB viral DNA was detected in blood, and blood smear showed no abnormal lymphocytes.

Rheumatic diseases: Common childhood rheumatic autoimmune diseases include lupus erythematosus, juvenile idiopathic arthritis, and dermatomyositis. Lymph node enlargement and vasculitis are common in rheumatism. However, other common clinical manifestations of rheumatic diseases were not observed, such as joint disease, muscle weakness, rash, and skin ulcer. Further, anti-nuclear antibody (ANA) and anti-double stranded (DS) DNA antibody tests were negative, the rheumatoid factor was normal, and four tests for vasculitis were negative. Vasculitis is a non-specific change. The anti-neutrophil cytoplasmic antibody (ANCA) was negative, so Wegener granuloma and other forms of vasculitis were excluded. As partial vacuities are difficult to identify, it is necessary to first exclude vasculitis caused by infection and tumor before rheumatic diseases can be diagnosed [4].

Other malignancies: Bone marrow smear showed no naive cells and bone marrow leukemia immune typing showed no obvious abnormal cell groups, so leukemia was excluded.

ALCL literature review

ALCL is a rare NHL first described in 1985 [5]. It is a proliferative disease of multiple large cell types resulting in nonspecific clinical but unique pathological, immune, and cytogenetic features. A number of clinical studies have found that ALCL has better prognosis than the other T-cell NHLs, but this has not been confirmed by a randomized controlled trial (RCT). ALCL accounts for about 10%-15% of pediatric NHL cases [6, 7].

According to the WHO classification, ALCL is divided into two subtypes: primary cutaneous ALCL, in which the tumor is confined to the skin, and systemic ALCL presenting with systemic disease [8]. In the pediatric population, primary cutaneous disease is very rare. Systemic ALCL has a bimodal distribution, with one peak in childhood and another in late adulthood.

ALCL is classified as clinical stage III and characterized by B group symptoms typical of an aggressive lymphoma, including fever, sweating, and weight loss. Lymph node enlargement is more common than in other NHLs. Extranodal lesions are also common, such as skin, bone, soft tissue, lung, mediastinum, and liver lesions, but these lesions rarely involve the intestines or CNS [9]. In the current case, tumor sites included cervical, mediastinal, and inguinal lymph nodes as well as the maxilla, thyroid, neck muscles, and surrounding soft tissue. Possible violation sites included pleura, pericardium, and liver, while there was no involvement of lung, brain, or bone marrow. There are often lytic bone lesions in ALCL, and imaging in this case showed bone destruction of the maxilla, so the invasion site included the maxilla [1, 2]. Histopathology confirmed tumor invasion of cervical lymph nodes, muscles, and soft tissues. As the brain was not involved, there was no disturbance of consciousness or other neurological symptoms, cerebrospinal fluid sediment smear exhibited no immature cells, and brain PET-CT revealed no lesions. Once the diagnosis of ALCL was confirmed, chemotherapy resulted in a marked reduction in neck and chest swelling.

Laboratory examination supported the diagnosis of ALCL. Dental radiography showed a widened periodontal membrane while CT showed (1) bone destruction in the left maxillary sinus and (2) infiltrative growth resulting in compression of surrounding tissues, including the right bronchus and superior vena cava. These imaging changes suggest a malignant disease. In addition, LDH was slightly elevated.

Tissue section were assessed by two independent hospital pathology departments and the final diagnosis of both was ALCL based on histopathological and immunocytochemical features. Histopathological features include dif-

fusely distributed large tumor cells with abundant cytoplasm and pleomorphic nuclei (such as horseshoe- and kidney-shaped forms) [10]. Histopathological findings were also typical of ALCL in this case, including focal necrosis of muscle tissue infiltrated with large round or oval tumor cells with irregular oval or reniform nuclei. Tumor cells were strongly CD30(+), ALK(+), CD43(+), EMA(+), and vimentin(+), less strongly BCL-6(+), and about 90% Ki-67(+). In contrast, cells were CD3(-), S-100(-), and CD56 (-). In general, ALCL tumor cells are CD30(+) and EMA(+) in most patients [11]. About 60%~85% of patients are also ALK(+), and about 60% express one or more T cell-associated antigens such as CD43 [12], but no T cell receptor signaling complex components such as CD3.

ALK is a tyrosine kinase receptor belonging to the insulin receptor family. Normally, it is distributed in nerve cells but not in lymphoid tissues [13]. ALK plays an important role in the development of brain and some specific neurons. About 53%~89% of ALCL cases have t(2; 5) (p23; q35) chromosomal translocation, resulting in gene fusion of ALK on chromosome 2 and NPM on chromosome 5. The NPMALK fusion protein promotes malignant transformation. Vimentin is a relatively specific marker for mesenchymal cell tumors, but it is also expressed in some lymphomas and epithelial tumors. Ki-67 can reflect the activity of cell proliferation, and high expression is related to invasion and metastasis.

One unique aspect of this case is that the mediastinal tumor resulted in respiratory and circulatory instability. Mediastinal space-occupying ALCL tumors are rare, accounting for only about 15% of all cases [2, 14]. The mediastinal tumor and enlarged mediastinal lymph nodes compressed blood vessels and trachea, necessitating high respiratory parameters to maintain breathing. Shock was caused by upper vena cava compression. Regular anti-infection, hormone, and symptomatic treatments were ineffective at stopping malignant progression, so the patient deteriorated to respiratory failure and shock many times, requiring emergency treatments.

Prognosis analysis

Expression of ALK is the most important known prognostic indicator of ALCL [15]. The survival rate of ALK(+) ALCL is significantly higher than that of ALK(-) ALCL [16], with 5 year survival rate of 71%~93% following chemotherapy [17]. The prognosis of CD56(-) ALCL is better than CD56(+) cases [13]. Elevated LDH suggests a high tumor load in NHL, and the prognosis is worse than normal. Mediastinum and (or) internal organ invasion are strong risk factors for poor outcome, as these patients have a high possibility of recurrence.

Disclosure of conflict of interest

None.

Address correspondence to: Dabo Liu, Guangzhou Women and Children Medical Centre, Guangzhou 510115, Guangdong, China. Tel: +8618818810919; E-mail: gzdaboliu@163.com

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