Kimura’s disease accompanied by mediastinal lymphadenopathy misdiagnosed as lung cancer: Case report and review of literatures

SUN Xi1, BAI Li1*, GAO Jie2
1Department of Oncology, 2Department of Pathology, General Hospital of PLA, Beijing 100853, China
*Corresponding author, E-mail:Baili0795@yahoo.com

[Abstract] Objective To further investigate the diagnostic pitfalls of Kimura’s disease (KD). Methods We report one case of Kimura’s disease accompanied with mediastinal lymphadenopathy admitted to General Hospital of Chinese PLA in the year 2010. After searching on PubMed and Chinese Medical Journal Searching Engines (Wanfang data base, Cqvip data base), we have found literatures reporting another 3 cases of Kimura’s disease with mediastinal lymphadenopathy. Plus the one we presented, all four patients’ clinical data were collected and analyzed thereafter. Up-to-date advancement on KD’s diagnosis and therapy would also be reviewed. Results Our case, a 61-year-old male, was initially misdiagnosed as lung cancer with mediastinal metastasis in 2008, but histopathology had confirmed only eosinophil infiltration in enlarged mediasinal lymph nodes, no malignant cells were identified. In the year 2010, he complained bilateral orbital masses, one of which was surgically removed, and was later confirmed as Kimura’s disease by histopathology. Clinical features of 4 patients, including our case and the other 3 retrieved in literatures, were available, 2 of whom were misdiagnosed as lung cancer while the other 2 as lymphoma in the beginning. All the 4 patients were responsive to steroid therapy. Conclusions Kimura’s disease could be associated with mediastinal lymphadenopathy which may confuse the physicians in diagnosing. Newly developed minimal invasive approaches such as endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) are helpful for the differential diagnosis.

[Key words] angiolymphoid hyperplasia with eosinophilia; lung neoplasms; mediastinum; lymph nodes

木村病伴纵隔淋巴结肿大被误诊为肺癌1例并文献复习

孙曦, 白莉, 高杰

[摘要] 目的 探讨木村病的诊断误区。方法 报道解放军总医院2010年收治的伴纵隔淋巴结肿大的木村病1例。在PubMed以及万方、维普等数据库搜索相关文献，查及木村病伴纵隔淋巴结肿大的病例3例。分析包括本例在内的4例患者的临床资料，总结近年来关于木村病的诊断及治疗方面的最新进展。结果 本例患者为61岁男性，最初于2008年诊断为肺癌，但组织病理学检查未见癌细胞，纵隔淋巴结内仅见嗜酸性粒细胞浸润。2010年患者因双侧眼眶肿物就诊，手术病理证实为嗜酸性粒细胞肉芽肿，即木村病。复习文献并加上本例在内，共获得4例合并纵隔淋巴结肿大的木村病患者的临床资料。其中2例误诊为肺癌，2例误诊为淋巴瘤。激素治疗对全部4例患者均有效。结论 木村病伴纵隔淋巴结肿大病例极其罕见，临床上易误诊。微创纵隔穿刺活检技术，如超声内镜和超声内镜引导下的经支气管针吸活检对鉴别诊断有帮助。

[关键词] 血管淋巴样增生，嗜酸粒细胞增多性；肺肿瘤；纵隔；淋巴结

[中图分类号] R551.121
[文献标志码] A
[文章编号] 0577-7402(2012)06-0486-06

Kimura’s disease (KD) is a rare, benign, chronic inflammatory disorder attributed to unknown cause, typically associated with subcutaneous head and neck mass, accompanied with bilateral cervical, axillary and groin lymphadenopathy. As far as we concerned, mediastinal lymphadenopathy, a very common condition in lymphoma, lung cancer, tuberculosis and sarcoidosis, has never been a specific clinical manifestation of KD. When KD presented as mediastinal lymphadenopathy, it
poses a diagnostic challenge to the physicians.

1 Materials and methods

A case of KD, initially presented as hilar mass and mediastinal lymphadenopathy, has been reported in present paper. At the beginning, the patient was misdiagnosed as lung cancer accompanied with mediastinal metastasis. The clinical files of this patient along with another 3 patients, who were diagnosed as KD accompanied by mediastinal lymphadenopathy as well, were analyzed. All the files of the other three patients were found by retrieving literatures from databases including PubMed, Wanfang (www.med.wanfangdata.com.cn) and Cqvip (www.cqvip.com) databases. The up-to-date advancements on diagnosis and therapeutic procedures of KD were be reviewed as well.

2 Case report and literature review

2.1 Case report

A 61-year-old male patient, admitted to General Hospital of Chinese PLA on June 12th, 2008, self-complained of fatigue, short of breath and a productive cough for four months. Before admission, he was diagnosed as lung cancer accompanied with mediastinal metastasis on account of thorax CT images at another hospital. Bronchoscopy, followed by a biopsy, revealed a lumen stenosis at the bifurcation of the right trachea. Chronic inflammation was then confirmed by pathologists, no malignant cell was identified by means of either cytopathologic or histopathologic detection.

On examination, he appeared comfortable, no weight loss had been noted since the illness, the temperature was 36.3 ℃, the blood pressure 143/90mmHg, the pulse 88 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 99% while he was breathing ambient air. Several small lymph nodes were palpable in right cervical region, and no tenderness was found. On auscultation of the lungs, breath sounds were diminished in intensity, more evident in lower parts bilaterally. The remainders of the exam were normal.

Apart from a slightly elevated squamous cell carcinoma-antigen (ScC) level of 12 μ g/L, other tumor-markers were in normal range. Cervical lymph node biopsy was later performed, however, histological study found nothing specific. A thorax CT scan obtained shortly after admission revealed a right hilar mass, 2cm × 3cm in size, and mildly enlarged lymph nodes in the mediastinum.

There were patchy air-space opacities in lower parts of the lungs, and bilateral moderate-size layering of pleural effusions as well (Figure 1). Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) was later performed in order to sample those enlarged mediastinal lymph nodes. Histopathology revealed a small number of lymph cells associated with various eosinophils infiltrated in blood vessels, but still, no malignant cells were identified (Figure 2).

The patient used to be a heavy smoker who consumed 2 packs of cigarettes a day. In addition, image study, an elevated
Scc level and his symptoms were strongly suggestive of lung cancer, but there had been no convincing evidence to establish the diagnosis. Piperacillin/tazobactam was then administrated intravenously. On hospital day 11, the patient claimed that he had been getting better, and was discharged on hospital day 21. Twenty days after dismission, the patient returned for further diagnosis and treatment. Thorax CT scan (Figure 3) showed that diffuse lung opacities could still be seen, yet they had been largely absorbed. All tumor-markers were within normal range, blood routine examination was generally normal, except an elevated eosinophilia ratio of 16.3% and an elevated serum IgE level of 783U/ml. Antibiotic therapy was changed to levofloxacin plus Piperacillin/tazobactam. Bronchoalveolar lavage was performed, but neither malignant cells nor eosinophils were identified. The patient was discharged 4 days after admission, he continued to cough productively but slowly resolving. During the next two years, he had been complaining intermittent cough with white sputum which was attributed to chronic bronchitis. No fever, dyspnea, weight loss had been noticed.

The patient had been closely followed by our clinic staffs. In March 2010, he was admitted to our hospital again due to symmetrical bilateral orbital masses associated with decreased vision and a dry throat. CT scans of orbital area and chest were performed shortly after admission. Pulmonary physicians and rheumatologists were invited for further diagnosis, both Sjogren’s syndrome and lung cancer were eventually ruled out owing to the laboratory test and image studies. Given that he was an aged man who had been suffering from respiratory disorders, the ophthalmologist finally decided not to surgically remove the both lesions, instead, they only resected the right one, treating the other with corticoid. The surgery went on smoothly on April 26th, 2010, and the specimen was sent for pathologic diagnosis. As is shown on HE slides: Abundant atrophic glands and irregularly shaped fibrosis with numerous eosinophils infiltrated(Figure 4).

Immunohistological staining was later performed, suggesting that ALK(−), BCL2(−), CD3(B-cell+), CD20(T-cell+), CD34(−), Ki67(<5%+), Kappa(−), Lambda(−), SMA(−) and CK(−). The pathologists eventually came up with the idea that it was consistent with eosinophilic lymphatic granuloma(ELG), namely KD.

Then the patient was prescribed with prednisone 5mg/d orally for the next month. Later on, another orbital CT scan(Figure 5) was performed, showing that the mass on the left side had been decreased enormously in size, there
Fig. 4  Histopathological study of surgically removed right orbital mass

Large amount of fibrosis (arrows) and diffuse eosinophil infiltration (Dotted arrows) were observed, the glandular structures partially remained. Such features were consistent with Kimura’s disease.

Fig. 5  Orbital CT images

A. Before surgery, there were bilateral orbital masses roughly with the same size; B. Two months after removing of the right orbital mass, treated with prednisone, there was no sign indicating a recurrence on the right side, and the mass on the left side shrank significantly.

was no sign indicating a recurrence on the right side, and he demonstrated that symptoms were abated. He had been healthy until December 2011.

2.2 Literature review  KD is typically associated with head and neck mass or regional lymphadenopathy in groin, axilla and cervical area. Mediastinal lymphadenopathy is an extremely rare occasion in KD, apart from this case, we have found only three cases of KD with a mediastinal involvement by searching in PubMed, Wanfang database and Cqvip database.

As is shown in Table 1, all patients were from East Asian countries, and there is also a male predominance, with a male/female ratio of 3:1, the average age is 51.75 (SD=12.04). Initially, two of the four were diagnosed as lymphoma while the other two were highly suspicious of lung cancer. All the four patients presented with cervical lymphadenopathy as well as mediastinal involvement and three of four had both an elevated serum eosinophils and IgE level, the other one patient’s laboratory study was not documented in the report (Table 2).

All the patients had received a steroid therapy and were all responsive. One had undergone radiotherapy, one had his right orbital mass surgically removed, and the other two patients received no further treatment. Although all the four patients were associated with mediastinal lymphadenopathy, only one (we herewith reported) had been confirmed eosinophils infiltration in mediastinal lymph nodes, and the other three cases were confirmed KD by means of cervical lymph node biopsy.

Out of the two patients who initially complained respiratory conditions like productive cough and thorax effusion, one went for clinic due to progressive fatigue, and the other went to the hospital simply hoping to rule out malignancy. Except for the patient from Japan whom we hadn’t been able to follow, the rest three patients had been in good health until December 2011, with no malignancy transformation or other complications.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Reported by</th>
<th>Sex</th>
<th>Age of onset (year)</th>
<th>Initial diagnosis</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sun et al</td>
<td>Male</td>
<td>61</td>
<td>Lung cancer</td>
<td>Henan, China</td>
</tr>
<tr>
<td>2</td>
<td>Zhang et al</td>
<td>Male</td>
<td>32</td>
<td>Lymphoma</td>
<td>Zhejiang, China</td>
</tr>
<tr>
<td>3</td>
<td>Wang et al</td>
<td>Female</td>
<td>62</td>
<td>Lymphoma</td>
<td>Taiwan, China</td>
</tr>
<tr>
<td>4</td>
<td>Kitasato et al</td>
<td>Male</td>
<td>52</td>
<td>Lung cancer</td>
<td>Fukuoka, Japan</td>
</tr>
</tbody>
</table>
3 Discussion

3.1 Definition and epidemiology  Kimura’s Disease (KD), a benign chronic inflammatory disorder with unknown etiology, was first described by Kim & Szeuto in 1937 as ‘eosinophilic hyperplastic lymphogranuloma’\(^5\). The disorder received its current name in 1948 when Kimura noted the vascular component and referred to it as an ‘unusual granulation combined with hyperplastic changes in lymphoid tissue’\(^5\).

Kimura’s disease is a relatively rare disease, and more endemic in east Asia, sporadic among Caucasians and Africans. Since 1984, over 450 cases have been reported in China\(^6\). There is a seemingly male predominance and is more evident between ages of 20-30.

3.2 Clinical manifestation  KD is characterized by painless subcutaneous masses in the head or neck region, often involves the parotid, submandibular or minor salivary glands. Less frequently, the eyelids, orbit and lachrymal glands may be involved, as well as the hard palate and larynx. In addition, it is often accompanied by regional lymphadenopathy such as axilla, trunk and groin, other rare locations include clavicle and is often accompanied by regional lymphadenopathy such as clavicle and

According to IASLC’s latest mediastinal lymph node map: #4 refers to paratracheal lymph nodes, #7 refers to subcarinal lymph nodes, #10 refers to hilar lymph nodes\(^18\). It is reported that nephrotic syndrome, which is a common complication for KD, is seen in approximately 15%–19% of cases\(^9\). The basis of this possible association is not well understood. On laboratory study, blood eosinophilia and markedly elevated level of serum immunoglobulin are the characteristic features of KD, which may have an elevated erythrocyte sedimentation rate (ESR) as well.

3.3 Diagnosis  KD’s image study used to be regarded as nonspecific. As previously stated, KD is mostly a head and neck disease. On image study, it often confuses with lymphoma or parotid malignancy. According to Park SW’s latest research on KD’s image conducted in 2011\(^{10}\), parotid and periparotid area were most frequently involved, more than half of the lesions located bilaterally and most of the lesions demonstrated mild or moderate enhancement on postcontrast CT scans and moderate or marked enhancement on postcontrast MR images. On PET scan, KD’s lesion presented as diffusely intense 18F-FDG uptake which is difficult to distinguish with metastasis malignancies\(^4\), Although KD’s image study has been improved, still, the diagnosis is dependent on histopathology.

On histological study, KD is characterized by the pattern of eosinophil infiltration, vascular endothelium and the presence of tight fibrosis. Lymphoid nodules with discrete germinal centers can occupy an area extending from the reticular dermis to the fascia and muscle. The fibrocollagenous part is combined with eosinophilic cells or eosinophilic ‘microabscesses’. Centrally, thick-walled vessels are present with hobnail endothelial cells. Immunohistochemical evaluation of the lymphoid nodules demonstrates a polymorphous infiltration of lymph nodes without clonality\(^11\). There have been intense dispute on whether Kimura disease and angiolympid hyperplasia with eosinophilia (ALHE) are the same entity of different stage. A number of pathologists have been convinced that KD is merely a chronic and deeper form of ALHE; however, most recent studies have distinguished them on account of clinical and histopathological characteristics. Epidemiologically speaking, ALHE is more endemic among western females. Histologically, ALHE seems to be an arteriovenous malformation with secondary inflammation while KD represents a primary inflammatory process with secondary vascular proliferation\(^4\).

According to the latest study on non-infectious causes of lymphadenopathy, reactive lymphoid hyperplasia (RLH), dermatoathic lymphadenitis (DLN), Rosai-Dorfman disease, Castleman disease and Kikuchi-Fujimoto disease are also needed to differentiate with KD, and cytomorphology would be helpful\(^12\). Some evidence has indicated that the interaction between Th1 and Th2 lymphocytes may lead to excessive eosinophilotropic cytokines productions, such as interleukin 4. Persistent antigenic stimulation from insect bites, parasitic infection, candidal infection, or viral infection may cause the activation of this cytokine pathway, but no consensus has been reached so far\(^4\).

3.4 Therapy and prognosis  Traditionally, there are mainly three methods to treat KD: Surgery, radiotherapy and steroid. The primary therapeutic selection is the surgery. As for lesions which have a clear boundary with no vascular involvement, complete resection should be performed. For those whose lesions could only be partially resected or those who are not surgery candidates, additional radiotherapy or steroid is required. Steroid therapy includes systemic therapy and regional therapy.
Recent years, new treatments, such as Gleevec, intravenous immunoglobulin and photodynamic therapy, have shown therapeutic effects on patients[16-18].

In the year 2005, Chen et al[16] first reported a case of Kimura’s disease which eventually evolved into Non-Hodgkin lymphoma (NHL). No other malignancy transformation has ever been documented since then. Most KD patients are responsive to steroid therapy, and some of them are even self-resolving[14,16,19]. Generally speaking, KD is a benign medical condition which has a good clinical prognosis.

3.5 About our case In our study, the patient was highly suspicious of lung cancer at the beginning, due to a hilar mass with mediastinal lymphadenopathy and an elevated tumor-marker level. However, after repeated biopsy procedures, no malignant cells were spotted. An elevated eosinophil level had raised our concern for eosinopilic pneumonia but this diagnosis was later ruled out due to the failure of finding eosinophils in a bronchoalveolar lavage. After reviewing histopathological reports of the enlarged mediastinal lymph node samples in 2008 and the specimen surgically removed two year later, pathologists ultimately concluded that their eosinophil infiltration patterns were generally similar. To our knowledge, this one is so far the first case of KD accompanied with mediastinal lymphadenopathy confirmed by histopathological study.

3.6 Diagnostic pitfalls Mediastinal lymphadenopathy is a common medical condition which could be seen in a variety of diseases. It prompts the idea of lung cancer, both small cell lung cancer(SCLC) and non-smaller cell lung cancer(NSCLC), lymphoma, tuberculosis and sarcoidosis[4]. Kimura’s disease has never been considered as a cause of that condition. In this study, including the case herewith reported, we overview 4 cases of KD associated with mediastinal lymphadenopathy altogether. It is possible that some cases, which were of the same pattern, might have gone unnoticed since lack of general application of the techniques of biopsy on mediastinal lymph nodes in the past. Although very few cases of KD accompanied with mediastinal lymphadenopathy have been documented so far, along with the development of minimal invasive procedures such as EUS-FNA and EBUS-TBNA, more such cases may be found in the future.

Kimura’s disease could be associated with mediastinal lymphadenopathy, although rare, which may confuse the physicians in diagnosing. Minimal invasive approaches, such as EUS-FNA and EBUS-TBNA are helpful to the diagnosis.

[References]

(Received: 2012-02-12 Revised: 2012-04-13)
(Edited by SHEN Ning, ZHANG Jin-tong)