CASE REPORT

Diagnostic dilemma: Kikuchi's disease or tuberculosis?

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SUMMARY

Any patient from a tuberculosis (TB) endemic area such as India with classical clinical features of fever, weight loss and lymphadenopathy, making a diagnosis of Kikuchi's disease (KD) prior to waiting for the 6-week culture is not appropriate. KD or histiocytic necrotising lymphadenitis is a rare self-limiting cervical lymphadenitis, often a diagnosis of exclusion. One needs to exclude TB, sarcodosis, lymphoma and autoimmune diseases to make such a diagnosis. The patient here with classical clinical presentation of TB with lymph node biopsy mimicking KD (biopsy and immunohistochemistry) posed a big diagnostic dilemma. However, culture of the biopsied lymphatic tissue was confirmed to be mycobacterium TB after the 6th week of incubation. The patient was treated with antitubercular drugs initially, and later, steroid was added in view of his persistent symptoms and he responded. One should wait for the tissue culture report to confirm or exclude the diagnosis of TB. Exclusion should not be based only on laboratory criteria. Histopathogically, TB can mimic any other granulomatous disorder.

BACKGROUND

Kikuchi's Fujimoto's disease is a benign self-limiting disease of the lymphoreticular system. The disease can be mistaken for tuberculosis (TB), lymphoma or systemic lupus erythematosus (SLE). The aetiology of Kikuchi's disease (KD) is unknown, although infectious and autoimmune aetiologies have been proposed. It generally presents as cervical lymphadenopathy and rarely with mediastinal lymphadenopathy. Systemic signs and symptoms may be associated with this disease. It is diagnosed by lymph node biopsy, which shows histiocytic necrotising lymphadenitis without any granuloma or caseation. One needs to exclude TB, sarcodosis, lymphoma and autoimmune diseases to give such a diagnosis. In TB endemic areas, one needs to be vigilant to give such a diagnosis because TB can mimic this disease.

CASE PRESENTATION

A 33-year-old patient was evaluated for low-grade fever and weight loss of 3 weeks' duration. Initially, fever was of low grade, but later fever spike increased and became intermittent associated with chills and night sweats. There were no histories of sore throat, cough, chest pain, breathlessness and burning micturition. On examination, the patient was of average build without pallor. There were no significant palpable peripheral lymph nodes or any cutaneous lesions. Systemic examinations were essentially normal.

INVESTIGATIONS

Initial investigation, which includes complete blood cell count with peripheral smear, was within normal limits. Peripheral smear for malaria parasite, serum Widal, blood culture, urine routine and urine culture were negative. Chest x-ray was normal. Intradermal Mantoux test was performed. The reading at 48 h was 30 mm with blisters all over (figure 1A,B). Sputum microscopy for acid-fast bacilli (AFB) was negative. Sputum culture was sent and was negative for AFB. Serum LDH was within normal limits. His erythrocyte sedimentation rate (ESR) was elevated and was 49 mm in the first hour (normal up to 30) and C reactive protein was positive. Ultrasonography of the abdomen did not confer any clue and was essentially normal.

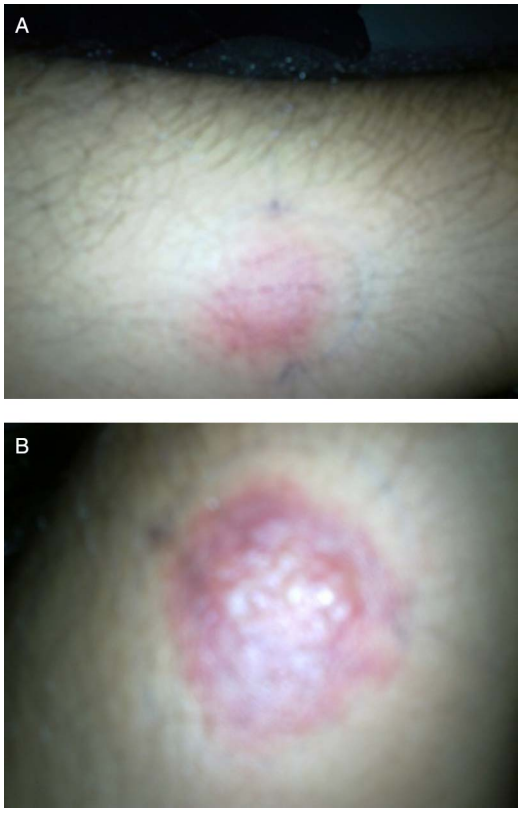

Figure 1 (A) Intradermal Mantoux test was performed, and the reading at 48 h was 30 mm erythema and induration. (B) The intradermal Mantoux test reading at 96 h was 30 mm erythema with blisters all over.

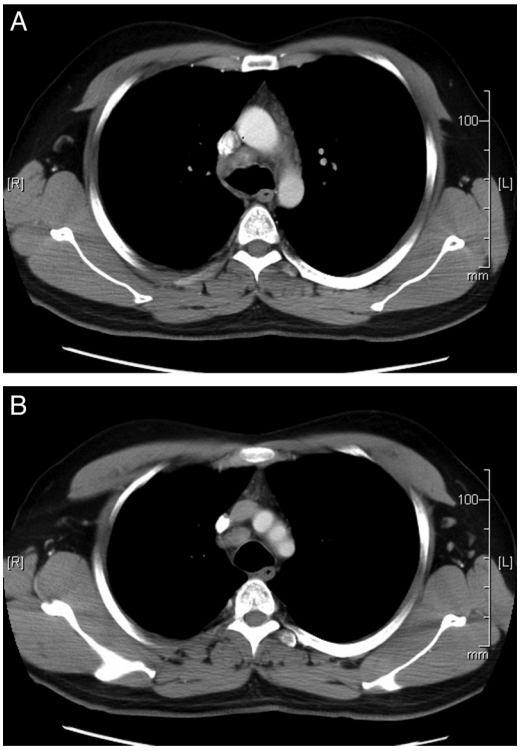

Figure 2 (A and B) Contrast-enhanced CT of the chest revealed enlarged mediastinal lymph nodes with some of them showing matting. Normal lung parenchyma and vasculature.

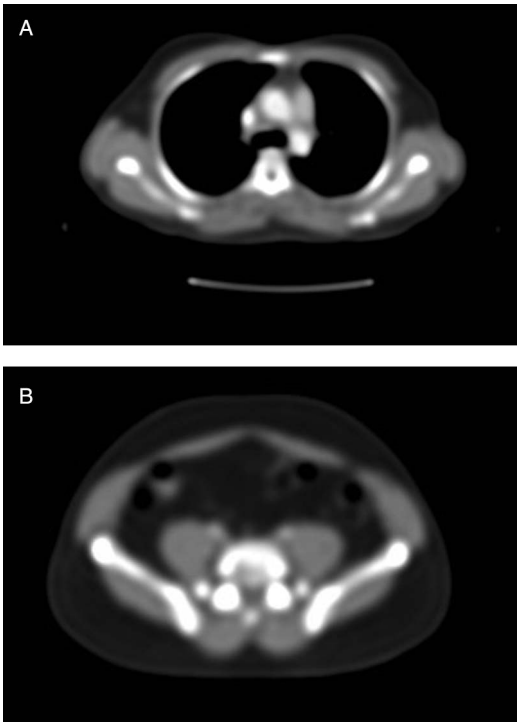

Figure 3 (A) Whole-body positron emission tomography-fluorodeoxyglucose (PET-FDG) scan performed revealed FDG avid nodes in the mediastinum. (B) Whole-body PET-FDG scan performed revealed FDG avid nodes in the precaval and paracaval regions representing active disease.

Contrast-enhanced CT of the chest revealed enlarged mediastinal lymph nodes with some of them showing matting (figure 2A,B), right paratracheal measuring 1.1×0.9 cm, 1.6×1.1 cm (matted), precarinal 1×0.9 cm (matted), subcarinal 2.1×1.4 cm and para-oesophageal 3.2×2.2 cm. Lung parenchymal was normal. There was no focal or diffuse interstitial or parenchymal lesion. Later, the whole-body positron emission tomography-fluorodeoxyglucose scan performed revealed fluorodeoxyglucose avid nodes in the mediastinum, right supraclavicular, precaval and paracaval regions representing active disease (figure 3A,B). There were no intracranial and pulmonary abnormalities. The liver, spleen, pancreas, kidneys, adrenals were unremarkable.

On histopathology, excision biopsy of the posterior cervical nodes revealed lymph nodes with numerous histiocytes and an increased number of apoptotic cells and cellular debris

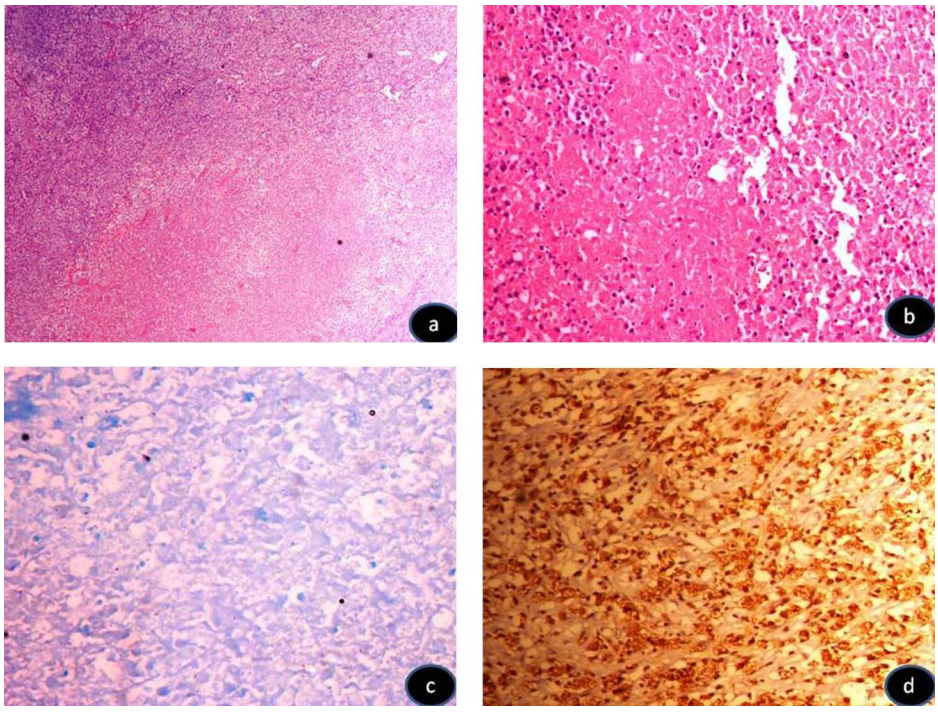

Figure 4 (A) (×100) and (B) (×200) On histopathology, excision biopsy of the posterior cervical nodes revealed lymph nodes with numerous histiocytes and increased number of apoptotic cell, cellular debris without neutrophil. (C) (×200) Tissue for acid-fast bacilli) was negative on Ziehl-Neelsen staining. (D)(×200) Immunohistochemistry of the biopsy tissue showed CD68 positive for histiocytes.

without neutrophils (figure 4A,B). Tissue for AFB using ZN (Ziehl-Neelsen) stain was negative (Figure 4C), and it was also negative by auramine-rhodamine staining using fluorescence microscopy. Immunohistochemistry showed CD68 positive for histiocytes (figure 4D). PCR for TB was negative. Lymph node samples were sent for *Mycobacterium tuberculosis* culture. The autoimmune screen was negative, as was the HIV and cytomegalovirus screens. Tissue culture in LJ media grown *M tuberculosis* at the 6th week of incubation. Drug susceptibility test using BACTEC-460 of the *M tuberculosis* isolate showed sensitivity to both isoniazid and rifampicin.

DIFFERENTIAL DIAGNOSIS

- Tuberculosis
- Hodgkin's disease
- Kikuchi's disease

TREATMENT

He was initially prescribed antipyretics and antibiotics but fever did not subside.

Later, he was started with standard 4 drug antitubercular (ATT) drugs based on strong clinical suspicion, radiological findings and Mantoux test. Since he was symptomatic even while he was on ATT for the past 3 weeks, as fever was not subsiding, a short course of naproxen was added in view ofKD, but no improvement in sign symptoms occurred. Finally, a short course of steroid (40 mg prednisolone daily for 2 weeks) was added to his ATT regimen. He became completely afebrile on the 8th day of steroid intake and steroid was stopped at 2 weeks without any tapering. The patient was continuing ATT since clinically TB was still suspected.

OUTCOME AND FOLLOW-UP

Patient was now on the continuation phase of ATT. He was afebrile at present, gained 5 kg in weight and had a very good appetite. A follow-up CT scan showed complete or partial regression of lymphadenopathy in 3 months.

DISCUSSION

The presentation of KD and TB almost overlap and it is difficult to segregate them clinically. Histopathologically, KD is characterised by cortical, paracortical necrosis with lymphoreticular infiltrate and the absence of granulocytic infiltrate. Still, an absence of these may not rule out KD completely.[1] Both may present with fever, upper respiratory sign symptoms, skin rashes, hepatosplenomegaly, weight loss, night sweats, anorexia, diarrhoea, vomiting and chest and abdominal pain. Though some sign symptoms may be less frequently seen in KD as compared to TB, therefore it poses a diagnostic dilemma to the treating physician. The exact aetiology of KD is unknown, though viral agents like Epstein-Barr virus, HIV, herpes simplex, human T lymphotropic virus1 and parvovirus may be associated.[2–4] Clinically, KD may mimic TB, SLE or lymphoma. Typical histology and immunocytochemistry may exclude lymphoma but not TB. Foamy macrophage in a biopsy specimen almost excludes lymphoma but needs a CD marker for confirmation.[4 5] However, lymphoma typically features cytological atypia and monomorphic cells. Features of KD that may help prevent its misdiagnosis as malignant lymphoma include incomplete architectural effacement with patent sinuses, presence of numerous reactive histiocytes, relatively low mitotic rates and absence of Reed-Sternberg cells.[6] Immunohistochemical stains are helpful in distinguishing KD from lymphomas. The large cells are negative for CD3 and CD20, which excludes the possibility of lymphoma, and they are positive for CD68, which demonstrates their histiocytic feature.[6] In this case, we excluded lymphoma and also SLE as all autoimmune markers were negative.[7]

The diagnostic and clinical dilemmas can be discussed. The patterns of lymphadenopathy in TB, KD and lymphoma are similar with a few differences. In KD, the lymph node size is not large (0.5–2.5 cm), mostly having unilateral cervical or jugular with perinodal infiltrate and karyorrhetic debris. These findings were present in this case which favoured KD more. Nodal necrosis may be found in both cases but favours TB more and was not present in this case. Mediastinal lymphadenopathy, though observed mostly in TB, was still reported in KD. Fine-needle cytology has a diagnostic accuracy of only 56%. In this case, diagnostic yield tissue in biopsy favoured KD, but clinically fever was persisting and not responding to non-steroidal anti-inflammatory drugs.[8–10] So clinically, a decision was taken to continue ATT as TB, being more common in the subcontinent, and the presence of mediastinal lymphadenopathy, weight loss, strongly positive Mantoux and benefit of not taking ATT will outweigh the risk. Routine laboratory investigation like ESR was elevated (49 mm) and CRP was positive. Final diagnosis was made after the tissue culture of the biopsied node. Patient improved on ATT. The follow-up CT scan showed complete or partial regression of lymphadenopathy in 3 months.

Is it possible to confirm the diagnosis of TB in the early stage using interferon-γ release assays (IGRAs) when mycobacterium culture is awaited? IGRAs do not help differentiate latent TB infection from TB disease. As with the tuberculin skin tests, IGRAs should be used as an aid in diagnosing infection with *M tuberculosis*. A positive test result suggests that *M tuberculosis* infection is likely; a negative result suggests that infection is unlikely. An indeterminate result indicates an uncertain likelihood of *M tuberculosis* infection. Although IGRA has a supportive role in making diagnosis of TB disease, in order to make a definite diagnosis of TB disease, we should wait for the culture report.[11]

In conclusion, although KD is uncommon, it should feature in a list of differential diagnoses of tender lymphadenopathy, especially that affecting the cervical region. One needs to exclude TB, sarcodosis, lymphoma and autoimmune diseases to give such a diagnosis. It is a challenge for a clinician to confirm as KD based on an initial biopsy report in a country where TB is endemic. One needs to wait for the tissue culture report to arrive at a final diagnosis.

Learning points

- Although Kikuchi disease (KD) is uncommon, it should feature in a list of differential diagnoses of tender lymphadenopathy, especially that affecting the cervical region.
- One needs to exclude tuberculosis (TB), sarcodosis, lymphoma and autoimmune diseases to give such a diagnosis.
- It is a challenge for a clinician to confirm KD based on an initial biopsy report in a country where TB is endemic. One needs to wait for the tissue culture report to arrive at a final diagnosis.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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