Ethambutol-resistant *Mycobacterium kansasii* cervical lymphadenitis in an immunocompetent adult patient: A case report and literature review

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1. Introduction

*Mycobacterium kansasii* is the second most commonly isolated of pathogenic non-tuberculous mycobacteria (NTM), after *Mycobacterium avium complex* (MAC) in patients with the acquired immunodeficiency syndrome (AIDS), and it is the most virulent [1]. *M. kansasii* usually causes lung disease. Extrapulmonary involvement is rare in immunocompetent adults, but does occur in immunocompromised children and in HIV-infected and other immunosuppressed adults [1–3]. *M. kansasii* is probably the easiest of NTM to treat effectively due to similarities with *M. tuberculosis*. *M. kansasii* is classically resistant to pyrazinamide (PZA) and sensitive to rifampin (RIF), isoniazid (INH), ethambutol (EMB), macrolides and aminoglycosides [4,5].

We report here a case of an adult immunocompetent patient with isolated supravacular lymphadenitis due to *M. kansasii* resistant to EMB, that was successfully treated with 12 months of RIF + CLR + INH therapy.

2. Case presentation

A 65-year-old male farmer with mild bronchiectasis was referred to our hospital with a 3 months history of asymptomatic neck mass. The patient was in a perfect state of health except for the cervical lump. He did not have serious infections in the past. A family history of opportunistic infections was not reported. Physical exam revealed a weight of 106 kg and an enlarged right supravacular tumor. The mass was soft and not painful to pressure with overlying erythema (Fig. 1A). Cervical-thoracic computed tomography (CT) confirmed the presence of right supravacular necrotic lymphadenopathy, 36 × 45.7 × 67 mm in diameter (Fig. 1B). No other CT cervical or thoracic lymphadenopathies or pulmonary lesions were observed except for mild bibasilar bronchiectasis. A fine needle aspiration (FNA) procedure was performed showing 1–9 acid-fast bacilli (AFB)/100 high power fields by Ziehl-Neelsen staining of the aspirated pus (Fig. 1C). FNA cytology showed granulomatous inflammation. Sputum Ziehl-Neelsen staining, quantitative PCR (qPCR) and culture in Löwenstein-Jensen medium were negative.

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negative for mycobacteria. A tentative diagnosis of tuberculous lymphadenitis was made and the patient was started on oral INH 300 mg + RIF 600 mg + PZA 1500 mg + EMB 15 mg/kg daily. Routine hemogram and biochemistry values were normal with an ESR of 25 mm/h, and C-reactive protein (CRP) of 0.7 mg/dL. Quantiferon TB Gold assay and HIV serology were negative.

Blood levels of IgG, IgM, IgA, complement proteins and granulocytes were normal. Fluorescent-activated cell sorter (FACS) analysis of lymphocytic subpopulations in peripheral blood was normal: CD3+ cells were normal. Fluorescent-activated cell sorter (FACS) analysis of TB Gold assay and HIV serology were negative.

300 mg + RIF 600 mg + CLR 500 mg/12 h, which was maintained for some months, disappearing along with the neck mass after the end of therapy. Seven months after the end of treatment he remains well.

3. Discussion

Ours is the 6th reported case of Mycobacterium kansasii extrapulmonary lymphadenitis in immunocompetent adults; 5 cases in children under 18 have also been reported. (Table 1) [6-14]. Sites of dissemination included cervical and mediastinal lymph nodes, skin, brain, soft tissue, joint, and peritoneum. Two patients had multiple non-nodal sites of involvement; one had concomitant Salmonella bacteremia suggesting an acquired defect in T cell immunity, and the work-up for immunodeficiency was not reported for the second case, who relapsed after treatment with INH, RIF and EMB [10,12].

Our patient had subtype I M. kansasii lymphadenitis, the subtype most frequently found in humans and the most pathogenic, but rarely isolated from the environment [11,15].

This is intriguing because he was a farmer and might be exposed to other serotypes of M. kansasii by outdoors exposure to contaminated soil and water, via aerosol or cutaneous contact or by drinking contaminated lake, river, or even tap water [1-3]. However, since the node was suprACLavicular, it is more likely to have spread from a lung focus not seen in the cervico-thoracic CT. Drinking contaminated spring water while farming or eating raw vegetables in contact with contaminated water or soil are other possibilities of having acquired M. kansasii infection by this patient.

Quantiferon–TB Gold test was negative in our immunocompetent patient. This is interesting because M. kansasii is one of the antigens making the Quantiferon–TB Gold test, a peptide cocktail stimulating the proteins ESAT-6, CFP-10 and TB7.7. The Quantiferon–TB Gold might be positive in M. kansasii infections [16]. However only 52% of the patients with M. kansasii disease were positive for the test in one Japanese study [17].

The M. kansasii strain from our case showed EMB resistance by microdilution, direct agar proportion and Etest drug susceptibility methods. CIP, LVX AMK, KAN, and TGC resistances were also observed. Very recently Bakulat et al. reported that M. kansasii EM resistance assessed by broth microdilution and Etest was observed in 83/85 (97.7%) of different subtypes (I to VI, I/II and IIB) of M. kansasii strains from 7 European countries and South Korea [18]. It will be of interest to determine if this high “in vitro” resistance of M. kansasii to EMB is confirmed in follow-up studies. Resistances to CIP (17/85, 20%) and CLR (1/85, 1.2%) were also reported in the same study.

A case of EMB and INH-resistant M. kansasii chronic tenosynovitis in an immunocompetent patient was reported in 2018 from the USA. The patient, with previous chemical hand skin damage had continuous exposure to a freshwater lake. He was cured with 6 months of CLR ± RIF therapy [19].

All the seven M. kansasii lymphadenitis cases in immunocompetent hosts reported in which the outcome was available were cured. Four of them received 6–18 months of EMB along with RIF and INH and/or CLR and two also underwent surgery with success. It is not clear presently that there is a gold standard therapy for M. kansasii infection. The use of rifampicin ± a macrolide seems reasonable with the potential addition of EMB [4]. However, the frequency of EMB resistance needs to be confirmed in additional studies. Some additional caution is also needed because although the European resistance rate to CLR is very low, a 26.8% resistance of M. kansasii subtype I to CLR has been recently reported from strains isolated in China [20].
<table>
<thead>
<tr>
<th>Reference/ Year</th>
<th>Country</th>
<th>Number of cases</th>
<th>Race</th>
<th>Age (years) /Gender</th>
<th>Symptoms</th>
<th>Lymphadenitis site involved</th>
<th>Other organs involved</th>
<th>Culture source</th>
<th>M. kansasii subtype</th>
<th>Comorbidities</th>
<th>EMB sensitivity</th>
<th>Therapy</th>
<th>Duration (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanlikama et al.1993</td>
<td>Turkey</td>
<td>2</td>
<td>European</td>
<td>13.3/NA</td>
<td>Neck mass</td>
<td>Submandibular</td>
<td>No</td>
<td>LN</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>INH + RIF + EMB</td>
<td>NA</td>
<td>Cure</td>
</tr>
<tr>
<td>Flint et al.2000</td>
<td>New Zealand</td>
<td>1</td>
<td>European</td>
<td>2.2/NA</td>
<td>Neck mass</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>EMB + CLR + surgery</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kob et al.2001</td>
<td>France</td>
<td>1</td>
<td>European</td>
<td>79/F</td>
<td>Fever, cough, itching, night sweats</td>
<td>Mediastinal</td>
<td>Skin</td>
<td>LN</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>INH + RIF + EMB</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>de Juan et al.2002</td>
<td>Spain</td>
<td>1</td>
<td>European</td>
<td>2/M</td>
<td>Neck mass + spontaneous fistula</td>
<td>Left lateral cervical</td>
<td>No</td>
<td>LN</td>
<td>NA</td>
<td>Sensitive</td>
<td>CLR + EMB</td>
<td>6</td>
<td>NA</td>
<td>Cure</td>
</tr>
<tr>
<td>Tabatabaie et al.2007</td>
<td>USA</td>
<td>1</td>
<td>European</td>
<td>74/M</td>
<td>Fever, somnolence, mental status changes</td>
<td>Left supraclavicular, paratracheal, pretracheal, hilar, Right parotid, submaxillary</td>
<td>No</td>
<td>LN</td>
<td>NA</td>
<td>Diabetes, alcohol abuse</td>
<td>Sensitive</td>
<td>INH + RIF + EMB</td>
<td>18</td>
<td>Cure</td>
</tr>
<tr>
<td>Salles et al.2007</td>
<td>France</td>
<td>1</td>
<td>European</td>
<td>56/F</td>
<td>Neck mass</td>
<td>Brain</td>
<td>LN</td>
<td>NA</td>
<td>Dietyesmia/ Salomea 09 (group D) infection</td>
<td>Sensitive</td>
<td>INH + RIF + EMB</td>
<td>18</td>
<td>Cure/ Relapse/ Permanent cure</td>
<td></td>
</tr>
<tr>
<td>Hsiao et al.2014</td>
<td>Taiwan</td>
<td>1</td>
<td>Chinese</td>
<td>67/M</td>
<td>Neck mass</td>
<td>Cervical, abdomen</td>
<td>No</td>
<td>LN</td>
<td>NA</td>
<td>Hypothyroism/ Salomea 09 (group D) infection</td>
<td>Sensitive</td>
<td>INH + RIF + EMB</td>
<td>18</td>
<td>Cure/ Relapse/ Permanent cure</td>
</tr>
<tr>
<td>Blanc et al.2016</td>
<td>France</td>
<td>1</td>
<td>Adult, NA age and gender</td>
<td>17/M</td>
<td>Neck mass</td>
<td>Cervical</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>11</td>
<td>Probable cure</td>
</tr>
<tr>
<td>Loizos et al.2018</td>
<td>Cyprus</td>
<td>1</td>
<td>European</td>
<td>65/M</td>
<td>Neck mass + post-FNA fistula</td>
<td>Right supraclavicular</td>
<td>No</td>
<td>LN</td>
<td>1</td>
<td>Bronchiectasis</td>
<td>Resistant</td>
<td>INH + RIF + CLR</td>
<td>12</td>
<td>Cure</td>
</tr>
</tbody>
</table>

INH = isoniazid; RIF = rifampin; EMB = ethambutol; CLR = clarythromycin; FNA = fine needle aspiration; NA = not available; M = male, F = female; LN = lymph node.
Availability of data and materials

The clinical, image and microbiological data supporting this work are included in the article.

Ethics approval and consent to participate

This was an observational study, in which the patient underwent routine clinical care for *M. kansasii* lymphadenitis, without any change in her patient's specific determinations or procedures. Therefore, no formal written informed consent was obtained from the patient. The Research Ethics Committee of the Principality of Asturias granted a formal waiver of ethical approval for this study.

The patients has signed a Hospital Universitario Central de Asturias (HUCA) written consent form for publication of his clinical data and images. Abiding by the Declaration of Helsinki the anonymity of the patient was preserved.

CRediT authorship contribution statement

**Víctor Asensi:** Conceptualization, Formal analysis, Data curation.

**Juan J. Palacios:** Funding acquisition, Formal analysis, Data curation.

**Maria Rivas-Carmenado:** Funding acquisition.

**Tomás Suárez-Zarracina:** Funding acquisition.

**Enrique Garcia-Carus:** Funding acquisition.

**Luis M. Fernández:** Funding acquisition.

**Héctor E. Torres:** Funding acquisition.

**Josha Fierer:** Writing - original draft, Writing - review & editing.

**José A. Carton:** Conceptualization.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

References


