CASE REPORT

Disseminated tuberculous lymphadenitis presenting as cervical mass in patient with HIV infection, worsening after antiretroviral initiation: diagnosis and treatment challenges

Alain Bruno Tagne Nouemssi

Family Medicine Residency
Department, NYMC at Saint
Joseph Medical Center, Yonkers,
NY, United States of America

Correspondence to
Dr. Alain Bruno Tagne Nouemssi,
dralaintagne@yahoo.fr

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SUMMARY

Tuberculosis (TB) continues to represent an important public health challenge in the world and the USA, especially given its association with HIV infection and population migration. Cervical tuberculous lymphadenitis represents the most common extrapulmonary presentation of TB in the USA. Considerations for other causes of neck mass often contribute to delay in diagnosis. In this report, we describe the case of a 41-year-old man who presented with painful swelling of the neck and was diagnosed with tuberculous lymphadenitis, complicated by HIV therapy-associated immune reconstitution syndrome. Prior to this diagnosis, he presented with a chronic intermittent cough, repeatedly treated as bronchitis. Furthermore, TB is a recognised occupational risk for primary care physician, as they are often the first contact for patients. With the Patient Protection and Affordable Care Act in the USA, the risk is likely to increase with the influx of newly insured often poor, and/or immigrants.

BACKGROUND

Tuberculosis (TB) is a contagious airborne disease caused mainly by *Mycobacterium tuberculosis* bacteria and transmitted through contaminated droplets from infected individuals. TB is primarily a lung disease, but extra-pulmonary localisations including lymph nodes are well documented. Extrapulmonary TB can occur alone or concurrently with pulmonary involvement, presenting a diagnostic challenge. Peto *et al*¹ reported a prevalence of about 10% to 15% of all reported TB cases worldwide. In the USA, about 20% of patients with TB have extrapulmonary disease, with lymphadenitis as presenting symptom in 30% to 40% of cases.² Also known as Scrofula, tuberculous lymphadenitis in the cervical region is among the most frequent presentations.³ It was initially described in children and adolescents, but with the HIV disease, the epidemiology and natural history of TB in general has changed. Currently, in developed countries, most cases are found in group age 20–40 years old, often HIV positive and immigrants populations.^{4 5} TB remains a global preoccupation for all countries, given the flow of populations from TB-endemic areas to places with sporadic cases. According to the Centre for Diseases Control

(CDC),⁴ one-third of the world's population is infected with TB, with about 1.5 million TB-related deaths worldwide. Furthermore, primary care providers serving immigrants and low-income communities, often presenting with misdiagnosed chronic cough are at increased risk for TB, especially given its HIV-linked resurgence.

CASE PRESENTATION

A 41-year-old man, recent emigrant from Africa, was referred to our hospital for intermittent fevers, chronic cough, lateral neck mass and positive TB skin testing (TST). He had been seen on two separate occasions at the outpatient clinic for persistent cough, treated as bronchitis. He returned to the clinic 5 months later, with sore throat, cough, fever and night chills. He also had a 1 month painful neck mass, increasing in size.

He appeared healthy, except for a 10×8 cm neck mass (figure 1). The mass was in the left posterior triangle of the neck, non-pulsatile, tender, with a central area of softening, extending posteriorly (figure 2). The right forearm showed a 20 mm positive TST. Oropharyngeal examination was normal with no bulging mass, erythema or swelling of tonsils. His lungs were clear to auscultation, and lymph nodes in axillary and inguinal area were enlarged. The patient was admitted for further management.

INVESTIGATIONS

HIV test was positive. Chest X-ray ruled out an active pulmonary TB infection. CT of the chest revealed a 1.5 cm paratracheal mass with right upper lung consolidative infiltrate, and bilateral pulmonary nodules. A neck CT without contrast showed pronounced bilateral lymphadenopathy of the neck, with unremarkable retropharyngeal space and submandibular/parotid glands. Puncture and TB testing were done. Sputum stain and cultures returned negative for TB. Meanwhile, CD4 count returned at 208, associated with HIV viral load above 1.5 million copies. A biopsy of the mass was later done and preliminary results from pathology was positive for acid-fast bacilli and later confirmed to be *M. tuberculosis*.

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Figure 1 Left-sided cervical neck mass (anterior view) covering retromandibular area and extending to the left ear posteriorly.

DIFFERENTIAL DIAGNOSIS

HIV-AIDS, lymphoma and TB were among the differential diagnosis. CT findings of cervical and thoracic lymph nodes were concerning for a neoplastic process, but TB remained a strong possibility. Abdomen CT with contrast revealed extensive lymphadenopathy, extending from periportal region and upper retroperitoneum through mesentery into the pelvis. Multiple nodes exhibited central hypoattenuation compatible with cystic degeneration or necrosis. These findings increased suspicion for a neoplastic process, leading to a biopsy of the neck mass.

TREATMENT

Broad spectrum antibiotics were started on admission. Antiretroviral therapy (ART) was delayed because of concern for immune reconstitution syndrome (IRS) in case of TB. After confirming the

Figure 2 Left-sided cervical neck mass (lateral view).

Figure 3 Neck CT showing multiloculated left cervical mass and right-sided necrotic lymph nodes (coronal view).

diagnosis of disseminated tuberculous lymphadenitis associated with AIDS, a four-drug regimen including rifampicin, isoniazid, pyrazinamide and ethambutol was started on day 7 of hospitalisation. Two weeks later, ART was also started. Following ART initiation, the patient's condition worsened, with a full week of daily fevers, chills, anorexia, extreme fatigue, 5.4 kg weight loss, shortness of breath and night sweats. A diagnosis of severe IRS was made after the patient became haemodynamically unstable, requiring intravenous fluid resuscitation. Following this phase, he improved exponentially with excess appetite and energy. In the meantime, the neck mass slightly decreased in size. With this improvement and after three consecutive negative sputum cultures the patient was discharged with HIV and TB treatment.

OUTCOME AND FOLLOW-UP

Ten days after discharge, the patient returned to the emergency room because of increasing pain and size of the same neck mass. He reported recurrent fevers, swallowing and breathing discomfort. A repeat neck CT (figures 3 and 4) done revealed multiple abscesses and bilateral necrotic lymph nodes. Peripherally enhancing collections were identified within the masticator space on the left, as well as prevertebra. Parotid and submandibular glands were distorted by the adjacent masses, with intact aerodigestive tract. Given the partial upper airways obstruction, patient was transferred to a tertiary centre. Follow-up revealed that no surgical procedure was performed. He received intravenous antibiotics, HIV and TB medications and was monitored for airway compression. His CD4 count improved to 367 cells/mL. After 3 weeks of hospitalisation without any significant change in the mass size, there was a spontaneous and abundant drainage of fluid from the neck. Spontaneous serosanguinous drainage

Figure 4 Neck CT showing multiloculated left cervical mass and right-sided necrotic lymph nodes (axial view).

continued for 3 days. The neck mass significantly decreased in size prior to discharge. He has remained stable on his medications, and the mass has completely resolved.

DISCUSSION

With the continued HIV epidemic, and migratory influx of populations from around the world, extrapulmonary TB now represents about one-fifth of cases of TB in the USA. Tuberculous lymphadenitis is the most common presentation of extrapulmonary TB, with the neck as a primary target. This patient's initial presentation posed a diagnostic and therapeutic challenge. Physicians should maintain a high index of suspicion in diagnosis of head and neck mass, especially in patients from TB endemic areas and/or immunocompromised. Syed *et al*⁶ described a case of cervical tuberculous lymphadenitis, initially diagnosed as metastases in a patient previously found with thyroid papillary carcinoma. Current recommendations by the American Association of Family Practice for diagnosis of cervical mass⁷ is to perform a fine-needle aspiration as the initial diagnostic procedure in HIV-positive patients and send for histology, Acid Fast Bacilli (AFB) stain and mycobacterial culture. However, there are risks associated with such procedure, especially formation of sinus tracts with external drainage or worse, an internal mass expansion with local risk for compression. This might explain the enlargement of the mass after discharge. On the other hand, initiation of ART is a known contributor to worsening of masses in immunocompromised patients⁸ and could also have contributed to the picture.

Indeed, paradoxical reactions defined as clinical and/or radiological worsening of pre-existing tuberculous lesions or development of new lesions in a patient who initially improves with anti-TB therapy, in the absence of relapse, have been described

starting in 1955 by Choremis *et al*.⁹ They reported that patients receiving treatment for TB occasionally developed exacerbation of fever and worsening of imaging. These findings were most frequently described in HIV-positive patients. This phenomenon is well known today and described as IRS, which is frequently seen in patients with extrapulmonary TB and disseminated TB. According to the CDC, IRS refers to a disease or pathogen-specific inflammatory response in HIV-infected patients that may be triggered by initiation or reinitiation of ART or by a change to a more active ART. Mortality from IRS during ART initiation remains low, despite a severe morbidity. Numerous parameters play a role in determining its impact, especially the severity of opportunistic diseases, the timing of ART initiation, the CD4 counts and comorbidities such as kidney failure. Current management strategies revolve around preventing IRS by the optimal timing of ART. However, a randomised controlled trial (RCT) done in South Africa showed that the use of steroids in some patients improve outcomes from TB-IRS.¹⁰ Others have reported on the role on anti-inflammatory drugs and immunomodulators, but no RCT has been conducted. Our patient developed a severe TB-IRS and was not a candidate for steroid use given his clinical status.

One of the main challenges in our case concerned appropriate timing of ART initiation. After years of debate, current recommendations by the WHO are to initiate ART in HIV-infected TB patients irrespective of their CD4 counts as this has the potential to reduce mortality. Treatment should not be interrupted in case of development of IRS, except in severe cases. These recommendations were based on the Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA), Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) and the Strategy Study of Immediate versus Deferred Initiation of Antiretroviral therapy or STRIDE (AIDS Clinical Trials Group A5221 strategy study of early vs later initiation of simultaneous ART and TB treatment initiation, ART initiated after TB treatment start but before its completion and finally ART after TB treatment). This latter study was stopped early because the mortality in both integrated treatment groups was 56% lower than in the sequential group.¹¹ This demonstrated that ART should be started before TB treatment completion, given the survival benefit, irrespective of CD4 counts.

The CAMELIA and STRIDE studies randomised individuals with confirmed pulmonary TB, HIV and CD4 cell counts, respectively, of <25 cells/mL and <77 cells/mL and compared

Learning points

- ▶ Tuberculosis (TB) remains a public health challenge and should be at the top of differential diagnosis, especially in patients from known endemic areas.
- ▶ With the HIV infection, there is a resurgence of TB, especially latent TB infection.
- ▶ Diagnostic can be challenging, especially when it has implications in the treatment initiation. While considering the possibility of a lymphoma as a differential for a mass, TB should be ruled out, especially in immunocompromised patients.
- ▶ Always be prepared for an immune reconstitution syndrome when initiating HIV treatment, with worsening of symptoms, before improvement.
- ▶ Optimal timing of antiretroviral treatment initiation in patients with TB is important to survival and improving morbidity.

immediate (within 2 weeks) and early (between 2 and 8 weeks) ART initiation to establish an optimal timing for ART initiation during TB treatment.¹² In the CAMELIA study, the mortality was decreased from 13% in the 2-week group to 8% in the 8-week group, while in the STRIDE trial, for patients with CD4 <50 cells/mL, 15.5% vs 26% of patients experienced AIDS or death in the immediate and early groups, respectively (p=0.002). All these studies concluded that starting HIV treatment soon after TB treatment improves outcomes.¹³ Contrary to these trials, a recent study (TB-highly active antiretroviral therapy) done in countries in the southern part of Africa on patients with confirmed TB, suggested that if CD4 count >220 cells/mL, ART can be delayed until 6 months of TB treatment.¹⁴ Currently, after reviewing these studies, a CDC expert panel recommendation is to start ART within 2 weeks of TB treatment initiation for ART-naïve patients with CD4 counts <50 cells/mL and within 8 weeks for those with higher CD4 counts.¹⁵ We appropriately started HIV medications at 2 weeks of TB treatment, given a CD4 count of 207 cells / mL.

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