CASE REPORT

Hepatic abscess as a paradoxical response to antituberculous chemotherapy for tubercular lymphadenitis

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SUMMARY

Tubercular liver abscess developing as a paradoxical reaction (PR) to antitubercular therapy (ATT) is relatively uncommon in the absence of disseminated disease and immunocompromised status of the host even in countries such as India where the disease is rampant. We report a rare case of hepatic abscess that developed paradoxically during antituberculous therapy for tubercular lymphadenitis in a 30-year-old woman who tested negative for HIV. Diagnosis was performed with the help of ultrasonography (USG)-guided aspiration of the abscess followed by cytopathological examination and PCR confirmation of the disease from the USG-guided aspirate. The patient responded well to oral corticosteroid therapy without any alteration of the ongoing ATT regimen. Details of the case and other relevant literature regarding the pathogenesis of this event are discussed in detail.

BACKGROUND

The phenomenon of paradoxical reaction (PR) developing after start of antitubercular therapy (ATT) in immunocompromised patients has been a well-known entity for years.¹ The intensity and timings of these reactions may vary at each incidence. They may be mild to very severe in presentation and may develop within days to months of starting the antituberculous chemotherapy. Such PRs have been reported in cases of pulmonary, pleural and lymph node tuberculosis.² To the best of our knowledge, development of a large hepatic abscess during successful chemotherapy for tubercular lymphadenitis in a HIV seronegative patient has never been reported on medline search. Diagnosis of such a PR is important as it raises a question mark over the successful containment of tubercular infection by appropriate chemotherapy in fresh cases of tuberculosis and sometimes poses a challenge in diagnosing other secondary infections and drug resistance to ATT, which can also mimic these PRs. We report this case to create awareness among physicians regarding the protean manifestations of these PRs during the course of ATT.

CASE PRESENTATION

A 30-year-old woman presented to our outpatient department with progressively increasing bilateral cervical and submandibular lymph nodes for the past 2 months. The largest of all the cervical nodes was inflamed, soft and swollen, and an impending

abscess was visible. The other lymph nodes were firm in consistency and non-tender, and showed signs of matting without abscess formation. All the routine haematological examinations were within normal limits except for a raised erythrocyte sedimentation rate (120 mm at the end of the first hour). A Mantoux test revealed an induration of 25 mm at the end of 72 h. Serology for HIV and other hepatitis markers was negative. Based on the clinical suspicion of tuberculosis, fine needle aspiration cytology was planned from the largest cervical lymph node, which revealed caseation in a background of multinucleated giant cells and lymphocytes. Prompt ATT was started. The patient was put on daily therapy of isoniazid (300 mg), rifampicin (450 mg), ethambutol (800 mg) and pyrazinamide (1000 mg), corresponding to the body weight of the patient. Progressive improvement was evident in the form of regression of size of the lymph nodes after around 2 weeks of ATT; the nodes were almost half in number and size at the end of the first month of ATT. The patient remained totally asymptomatic until the completion of an intensive 2-month phase of therapy when suddenly, 1 day, she experienced a dull aching right hypochondrial pain and postprandial abdominal distension coupled with mild continuous fever and feeling of dyspepsia. Gastro-oesophageal reflux was suspected and the patient was given proton pump inhibitors (40 mg daily); however, there were no signs of improvement in her symptoms.

INVESTIGATIONS

Liver function tests remained within normal limits. On examination, a slightly enlarged liver was palpated. Ultrasonography (USG) revealed mild hepatomegaly with presence of liver abscess in the right lobe of the liver in the form of a thick-walled area with low-level echoes and organised areas measuring 63×60×67 mm with a volume of 135 cc ([figure 1](#)); subsequent USG-guided aspiration was planned. CT scan of the abdomen also confirmed the presence of a right liver lobe abscess, and the remaining abdominal organs were reported to be normal in echotexture and size. USG-guided aspiration was performed with a thick bore needle and the pus was sent for cytopathological examination, which revealed a tubercular picture in the form of multinucleated giant cells and a large number of lymphocytes against a background of ongoing caseating necrosis ([figure 2](#)). Culture for acid

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Figure 1 Ultrasonography of the liver showing abscess in the right lobe of the liver in the form of a thick walled area with low level echoes and organised areas measuring 63×60×67 mm.

fast bacilli using the BACTEC method revealed *M. tuberculosis*. Drug susceptibility testing was carried out after culture using the resistance ratio method, which revealed sensitivity to both isoniazid and rifampicin. Growth of bacilli in culture was a confirmation of a tubercular liver abscess developing paradoxically in response to antitubercular chemotherapy for cervical lymphadenitis. PCR also tested positive for *M. tuberculosis*.

DIFFERENTIAL DIAGNOSIS

Amoebic liver abscess and pyogenic liver abscess were among the differential diagnoses.

TREATMENT

Based on a suspicion of PR, the patient was put on oral prednisolone therapy (40 mg daily), which was gradually tapered over 1 month. The patient was taking a continuation phase of ATT during this event of PR. An excellent response to corticosteroid therapy was observed clinically and radiologically, as USG after 1 month revealed a normal echotexture of the liver and bile ducts (figure 3). The patient completed 6 months of ATT during which there was a complete regression of the cervical and submandibular lymph nodes.

OUTCOME AND FOLLOW-UP

The patient completed 6 months of ATT with no future recurrence of disease and no adverse PR.

DISCUSSION

PR in TB is defined as transient worsening of sign and symptoms, or the appearance of a new lesion after beginning of appropriate ATT, which may not necessarily warrant a change of ongoing drug therapy. Paradoxical liver abscess of tubercular

aetiology is a rare entity in a non-HIV positive individual. These abscesses can occur anywhere between 2 and 12 weeks after starting antituberculous chemotherapy. A liver abscess developing as a paradoxical response after ATT for peritonitis has been previously reported,³ but no case of a hepatic abscess developing after ATT for tubercular lymphadenitis was found on a medline search. Tubercular liver abscesses are seen rarely and have a prevalence of only 0.34%, even in patients with hepatic tuberculosis.⁴ The pathogenesis of these PRs is mainly immune mediated, and it has been postulated that active TB can result in immunosuppression through an altered cell-mediated response; and once the active tuberculosis comes under control after chemotherapy, focal immune responses get enhanced, which is also known as immunological rebound, leading to the recruitment of lymphocytes and macrophages at the site of the lesions. These lesions further enlarge and become evident as abscesses.⁴ Another factor responsible for worsening of the disease is hypersensitivity to the tubercular proteins released from killed TB bacilli.⁵ These lysed cell wall products in turn accelerate the production of tumour necrosis factor α , and interleukins-2, 6 and 8, which enhances the local inflammation causing further caseation and necrosis leading to expansion of pre-existing tubercular foci in the liver, resulting in abscess formation. Once tuberculosis comes under control, the level of immunosuppression resolves and there is enhancement in the levels of type IV hypersensitivity (immunological reconstitution). If culture is taken during this phase, a slight positivity may be found due to some metabolically dormant live bacilli (persisters) in the old pre-existing lesions, which have become metabolically active now, rendering the culture from the PR sites positive. PRs showing positive cultures for *M. tuberculosis* have been reported previously.^{6,7} In the present case, the patient developed features of paradoxical hepatic abscess 8 weeks after beginning ATT. There was a significant improvement in the primary pathology (tubercular lymphadenitis), as evident by the reduced size of the cervical nodes and weight gained by the patient. These clinical improvements, supported by sensitivity of bacilli to isoniazid and rifampicin, excluded the possibility of drug resistant bacilli and provided a clue in favour of a PR. There should always be a very high index of suspicion to make an early diagnosis of a paradoxical reaction. A paradoxical liver abscess developing after ATT is mostly missed in countries such as India because of the very high incidence of pyogenic and amoebic liver abscess, which leads to a delayed diagnosis of these reactions. Cytopathological examination of the USG-guided pus aspirate can help in confirming the aetiology. Culture and PCR have

Figure 2 Cytopathological examination revealing multinucleated giant cells and a large number of lymphocytes on a background of ongoing caseating necrosis.

Figure 3 Ultrasonography after 1 month revealed a normal echotexture of the liver and bile ducts.

always been the gold standards. However, these immunological lesions have a poor yield for mycobacterial culture; however, our case culture using the BACTEC method revealed growth of *Mycobacterium tuberculosis*. These lesions always show a tremendous response to corticosteroid therapy.⁸ Meanwhile, a clinician should also rule out drug resistant TB, non-tubercular mycobacteria infection and other infective causes that may be responsible for these events before starting corticosteroid therapy for PRs. The addition of corticosteroid therapy and continuation of the same ATT regimen can lead to complete recovery of the patient, as in our case.

We strongly emphasise that worsening of a primary tubercular lesion or development of another lesion during ATT may not always indicate treatment failure, and warrants a change of

treatment; in our case, it definitely indicated development of an immunologically mediated PR, which can be very frustrating for the treating clinician.

Interferon γ release assay can play an important role in making the diagnosis of latent tubercular foci in countries having a high burden of tuberculosis.⁹

Competing interests None declared.

Patient consent Obtained.

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Learning points

- ▶ An adverse reaction during the course of antitubercular therapy should not be considered as treatment failure or drug resistance.
- ▶ Diagnosis of a paradoxical reaction is made only after excluding the possibility of drug resistant tuberculosis (by drug susceptibility testing), co-existent secondary infections and adverse drug reactions.
- ▶ Corticosteroid therapy remains the gold standard treatment for the management of paradoxical reactions.

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