Isoniazid-resistant intracranial tuberculoma treated with a combination of moxifloxacin and first-line anti-tuberculosis medication

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Received 1 July 2010
Accepted 8 June 2011

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We report a case of a previously healthy 23-year-old Somalian care assistant. She presented with a 4 month history of persistent occipital headaches associated with intermittent nausea and vomiting. Computed tomography and magnetic resonance imaging of the brain showed a large enhancing lesion in the right cerebellar hemisphere with surrounding ring lesions, suggestive of an intracranial neoplasm with metastases. However, tuberculoma of the brain was confirmed based on histology of the excision biopsy and cerebrospinal fluid (CSF) culture results: Mycobacterium tuberculosis resistant to isoniazid (INH) with sensitivity to other standard drugs, including fluoroquinolones, was cultured from CSF. No primary focus to suggest spread from elsewhere was found. The patient was treated successfully with moxifloxacin, rifampicin, pyrazinamide and ethambutol. Isolated INH-resistant intracranial tuberculoma is rare in adults. It can mimic other intracranial masses and should be kept in mind, especially in populations with a high risk of tuberculosis. Clinical use of moxifloxacin in INH-resistant tuberculomas is limited in humans and this case demonstrates that moxifloxacin may be an effective alternative treatment.

Introduction

Intracranial tuberculomas are uncommon in developed countries and can be a diagnostic challenge because they present in a similar way to other intracranial lesions such as gliomas and meningiomas. Intracranial tuberculomas are seen in about 1% of all patients with tuberculosis (TB) (Abuhamed et al., 2008) and can account for 0.5–30.5% of all intracranial space-occupying lesions (Tiwari et al., 1989). Treatment can be difficult in some cases, as some first-line anti-TB drugs penetrate the brain poorly and not all tuberculomas are fully sensitive to first-line anti-TB drugs. Isoniazid (INH) and pyrazinamide penetrate the blood–brain barrier easily, whilst rifampicin and ethambutol penetrate less easily (Rock et al., 2008). Fluoroquinolones such as moxifloxacin are important second-line agents, but treatment of INH-resistant tuberculomas with moxifloxacin is limited in adults. We report a case of an INH-resistant intracranial tuberculoma mimicking an intracranial neoplasm that was treated successfully with moxifloxacin in combination with rifampicin, ethambutol and pyrazinamide.

Abbreviations: AFB, acid-fast bacilli; ATT, anti-tuberculosis treatment; CSF, cerebrospinal fluid; CT, computed tomography; CXR, chest X-ray; INH, isoniazid; MRI, magnetic resonance imaging; MTB, Mycobacterium tuberculosis; TB, tuberculosis.

Case report

A 23-year-old Somalian care assistant presented with a 4 month history of persistent occipital headaches associated with intermittent nausea and vomiting. There was no history of visual symptoms or diplopia. Neurological examination revealed only hyperreflexia on the left side. The rest of her clinical examination was unremarkable. Chest X-ray (CXR) was normal. Computed tomography (CT) (Fig. 1) and magnetic resonance imaging (MRI) (Fig. 2) of the brain showed a large enhancing lesion in the right cerebellar hemisphere with a number of surrounding ring lesions. There was also displacement of the fourth ventricle with moderate displacement of cerebellar tonsils through the foramen magnum. The initial impression at that point was of an intracranial neoplasm with metastases. Excision biopsy was rapidly undertaken and the cerebellar lesion with a surrounding ring lesion was excised. However, the histology showed gliotic tissue with inflammatory infiltrate of caseating granulomata, some with a surrounding area of necrosis and giant cells. There was no evidence of malignancy. Stains for acid-fast bacilli (AFB) were positive (Fig. 3). Cerebrospinal fluid (CSF) taken during the operation was AFB-negative, but PCR for Mycobacterium tuberculosis (MTB) complex was positive. The patient denied any previous history of TB, but revealed possible...
exposure 1 year previously. Her CXR did not suggest any evidence of current or previous TB and a primary focus to suggest spread from elsewhere was not demonstrable. She was commenced on standard anti-TB treatment (ATT) and corticosteroids whilst awaiting her final CSF-culture results. Her final CSF culture grew MTB resistant to isoniazid (INH), streptomycin and prothionamide. It was sensitive to other standard drugs, including the quinolones moxifloxacin, ciprofloxacin and ofloxacin. INH was stopped and moxifloxacin (400 mg once daily) was added to her ATT of rifampicin, pyrazinamide and ethambutol. Follow-up CT at 3 months and MRI after 9 months treatment showed a good post-operative result with no recurrence. She remains under regular follow-up and continues to remain well on her treatment.

Discussion

Numerous case reports of intracranial tuberculomas from a distant focus have been reported (Abuhamed et al., 2008). Isolated INH-resistant intracranial tuberculomas have been described in children (Sermet-Gaudelus et al., 1999), but they are uncommon, and are even rarer in adults. We believe that this is the first reported case of an isolated INH-resistant cerebral tuberculoma in an adult. Tuberculomas are thought to arise when tubercules in the brain parenchyma enlarge without rupturing. Tuberculomas can thus occur in the absence of TB meningitis. Most tuberculomas are solitary, but 15–24 % are multiple (Hejazi & Hassler, 1997). About 50 % of reported cases of tuberculoma have had a past history of TB or evidence of current TB (Ramamurthi & Varadarajan, 1961; Anderson & Macmillan, 1975). Our patient did not have any history of TB.

Clinical presentation is non-specific, mainly due to the varying size and location of the tuberculoma. Patients can present with headaches, seizures and other signs of raised intracranial pressure, such as papilloedema and focal neurological deficits related to the site of the lesion (Seow et al., 1991). CT and MRI are the most common radiological investigations undertaken. On CT, radiological features vary according to the stage of the tuberculoma. A mature tuberculoma appears as a well-demarcated ring-enhancing mass, as with our patient. Immature tuberculomas are iso-to hyperdense on plain CT and show ring enhancement with contrast. MRI appearances also vary. Lesions with central caseation show central hypointensity on T2-weighted imaging, whereas more solid, non-caseating tuberculomas appear hyperintense (Abuhamed et al., 2008). However, other intracranial lesions, such as gliomas, meningiomas, neurocysticercosis and intracranial metastasis, can appear very similar (Lee et al., 2002).

CSF from patients with tuberculomas without meningitis is usually smear-negative (Talamás et al., 1989). MTB
complex PCR assay on CSF can be used to make a diagnosis and has been recommended as a routine tool for the rapid diagnosis of tuberculoma of the brain (Singh et al., 1999). Studies have shown sensitivities of PCR on CSF ranging from 60 to 75% and specificities of 90–95% (Davies et al., 2008). Ultimately, histology is usually required to distinguish whether this is infectious or malignant and some studies recommend this before commencing ATT (Abuhamed et al., 2008). This can be obtained either by CT-guided biopsy, which is more suitable for small, deep-seated tuberculomas that can be treated medically, or by surgical excision.

Most tuberculomas can be treated with anti-TB chemotherapy. The duration is usually a prolonged course; the optimal duration is debated and some recommend 18–24 months. The American Thoracic Society (ATS, 2003) and UK National Institute for Health and Clinical Excellence (NICE, 2006) guidelines recommend a treatment course of 12 months. INH, rifampicin and pyrazinamide should be given in the first 2 months with a fourth drug: options include ethambutol, ethionamide and streptomycin intramuscularly (intrathecal administration is no longer recommended). Ethionamide is potentially teratogenic and streptomycin is potentially ototoxic to the fetus; both should be avoided in pregnancy (Davies et al., 2008).

In cases where there is INH resistance (as in our case) or intolerance, second-line agents such as fluoroquinolones are an option (ATS, 2003). However, clinical use of moxifloxacin in intracranial tuberculomas in adults is limited. From our literature search, there has only been one reported study of moxifloxacin use in a case of cerebral tuberculoma with tuberculous meningitis and miliary TB (Alfenaar et al., 2008). This patient developed axonal polyneuropathy from suspected INH toxicity, causing impairment in his walking. INH was stopped and moxifloxacin was used instead, with monitoring of the levels in the CSF. When a dose of 400 mg once daily was used, CSF moxifloxacin levels were found to be 94% of those in serum. The patient made a good initial response after commencement of moxifloxacin, with partial improvement in his walking impairment. In our case, the same dosage of moxifloxacin was used and our patient made a complete recovery with no signs of recurrence, which suggests that moxifloxacin may be of benefit in the treatment of INH-resistant cerebral tuberculoma.

In conclusion, isolated INH-resistant cerebral tuberculomas are rare in adults. They can mimic other intracranial masses and should be kept in mind, especially in populations with a high risk of TB. Treatment with moxifloxacin in combination with rifampicin, ethambutol and pyrazinamide was successful. We feel that moxifloxacin is an effective alternative treatment in cases of intracranial tuberculomas with INH resistance; however, further studies in larger populations are necessary to confirm this.

Acknowledgements

We would like to thank Dr I. Scott for his help with the histology slides.

References