Reminder of important clinical lesson

Sulphadiazine-induced renal stones in a 63-year-old HIV-infected man treated for toxoplasmosis

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Summary

A 63-year-old man was admitted for investigation of blurred vision and multiple ring-enhancing lesions on cranial MRI. Histopathological examination of tissue obtained at brain biopsy showed multiple *Toxoplasma gondii* cysts. He was started on a combination of sulphadiazine and pyrimethamine for cerebral toxoplasmosis and was subsequently diagnosed with HIV-1 infection. He then developed acute renal failure and flank pain and was diagnosed with bilateral vesico-uretric calculi requiring bilateral stent insertion. The retrieved renal calculi were negative for the common stones that are routinely tested for in our laboratory and had the macroscopic characteristics of a sulphadiazine stone. His renal failure responded to cessation of the sulphadiazine.

BACKGROUND

This case highlights first the importance of considering HIV infection in older patients, especially in the setting of cerebral ring-enhancing lesions, and second that clinicians need to be aware of the risks of drug-induced renal calculi when using medications such as sulphadiazine.

CASE PRESENTATION

A 63-year-old man presented with blurred vision of several weeks duration without focal neurological symptoms. He had a background history of glaucoma and dyslipidaemia. He lived with his wife, was a non-smoker and had two grown children. Visual field examination revealed a left homonymous haemianopia while the rest of the neurological, respiratory, cardiovascular and gastrointestinal examination was unremarkable.

INVESTIGATIONS

Full blood picture, inflammatory markers, renal, liver function and chest x-ray were normal. Contrast CT of the head showed a ring-shaped lesion in the right infero-temporal area with MRI showing multiple supra-tentorial and infra-tentorial peripherally enhancing lesions (figure 1). Stereotactic brain biopsy of the right temporal lobe lesion was performed and intraoperative sections showed infiltration by lymphocytes and histiocytes with areas suggestive of necrosis secondary to focal lymphocytic vasculitis. Histology of paraffin sections identified numerous *Toxoplasma* cysts and *Toxoplasma gondii* PCR from the brain biopsy was positive.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in a case such as this without known immunocompromise is relatively narrow with secondary neoplasm being the most likely diagnosis. Infections such as tuberculosis, neurocystercosis, progressive multifocal leucoencephalopathy (PML) and

toxoplasmosis are less likely without risk factors for these infections or evidence of immune deficiency. Inflammatory diseases such as neurosarcoid may also occasionally cause ring-enhancing lesions. In the setting of HIV with significant immune compromise, cerebral toxoplasmosis and primary central nervous system (CNS) lymphoma become more likely, although most of the above-mentioned aetiologies occur more frequently in HIV-positive patients.

TREATMENT

He was started on intravenous sulphadiazine 1 g 6 hourly and oral pyrimethamine 25 mg daily. Given the diagnosis of toxoplasmosis an HIV test was performed which

Figure 1 T2 fluid-attenuated inversion recovery MRI coronal section showing oedema around ring-enhancing lesions.

Figure 2 CT of the renal tract showing bilateral vesico-ureteric calculi (arrows).

confirmed HIV-1 infection. Lymphocyte subsets revealed a very low CD4 T-cell count of 6×10^6 cells/ml (1%) with a CD4:CD8 ratio of 0.01. The HIV-1 viral load was 6607 copies/ml. A diagnosis of SIADH was made (serum sodium 128 mmol/l; plasma osmolality 269 mmol/kg; urine sodium 199 mmol/l; urinary osmolality 655 mmol/kg) and he was put on 500–1000 ml/day fluid restriction.

OUTCOME AND FOLLOW-UP

Antiretroviral therapy was postponed during the induction phase of cerebral toxoplasmosis treatment due to the potential risks of immune reconstitution syndrome. One week after starting sulphadiazine, he developed oliguria, flank pain and acute renal failure with serum creatinine rising from 65 to 205 $\mu\text{mol/l}$ within 2 days. Renal ultrasound showed minor dilatation of the right pelvicalyceal area and CT of the renal tract confirmed bilateral vesico-ureteric stones with bilateral renal pelvic dilatation (figures 2 and 3). Bilateral retrograde JJ stents were inserted with retrieval of several calculi (figure 4). Common renal stone constituents including calcium oxalate, calcium phosphate, cysteine, uric acid, magnesium and ammonium sulphate were negative. His creatinine was slow to improve despite adequate rehydration and the sulphadiazine was substituted with clindamycin 5 days after stent insertion. Four days after ceasing the sulphadiazine, his creatinine had normalised.

Figure 3 CT of the renal tract showing bilateral hydronephrosis.

Figure 4 Ureteric stones obtained at insertion of JJ stent (scale in cm).

DISCUSSION

The pathogenesis and natural history of HIV infection are well understood. However, the diagnosis is often overlooked, especially in older patients who do not fit a high-risk demographic. Although 60% of new HIV and AIDS diagnoses are made in the 20–40-year-old age bracket, 9.7% of all new HIV-1 diagnoses and 15.1% of AIDS cases in Australia occur in the over-50 age group.¹ Older patients are significantly more likely to be diagnosed later and have a significantly higher mortality than younger patients.² The differential diagnosis for multiple ring-enhancing lesions in the brain includes primary CNS lymphoma, primary or secondary non-lymphomatous neoplasms, neurosarcoidosis, abscesses (including toxoplasmosis, cryptococcosis and tuberculosis) and rarely PML.³ Most of these diseases are seen with increased frequency in patients with HIV/AIDS.

This case highlights an important issue in investigation of cerebral ring-enhancing lesions. With established HIV infection, positive Toxoplasma serology and multiple ring-enhancing lesions, current expert opinion is to treat empirically with anti-toxoplasma therapy and only perform a brain biopsy if there is no clinical or radiological improvement at 2 weeks.⁴ Identification of HIV infection in this case may have avoided a brain biopsy, and HIV testing should be considered routinely in the diagnostic work-up of any patient with multiple ring-enhancing lesions.^{4–5} Importantly, the absence of absolute lymphopenia on a full blood count cannot be used to exclude HIV infection with significant immunosuppression. The negative predictive value of a total lymphocyte count $<1.2 \times 10^9/\text{l}$ for a CD4 count of <200 cell/ mm^3 in the setting of HIV infection is only 38%.⁶

High-dose sulphadiazine is considered as a first-line therapy in HIV-associated Toxoplasma encephalitis. The reported incidence of sulphadiazine-induced acute kidney injury ranges from 0.4% to 29%.⁷ The majority of these cases are thought to be due to renal calculi.⁸ Sulphadiazine stones often have a characteristic amber colour with radial striations, which may be useful to distinguish them from other crystals.⁷ The majority of sulphadiazine-induced stones contain the poorly soluble metabolite *N*-acetylsulphadiazine rather than sulphadiazine itself.⁹

Drug-induced renal calculi have been shown to represent up to 1–2% of all renal calculi analysed in specialised laboratories. Common drugs implicated include

antimicrobial sulphonamides (including sulphadiazine), indinavir, triamterene, acyclovir and methotrexate. Ciprofloxacin, orlistat, oral sodium phosphate solution and atazanavir have also been implicated.⁷ The majority of drug-induced renal calculi are radiolucent on plain films.⁹ Although patients may present with frank renal colic, the presentation is often subclinical. As was present in this case, both high medication dose and dehydration are risk factors for sulphadiazine-associated nephrolithiasis. Prevention of crystal formation includes vigorous hydration. With the onset of symptoms or worsening of renal function, consideration should be given to alkalinisation of the urine with sodium bicarbonate or switching to an alternative agent.⁷ In severe cases that do not respond to these measures, dialysis may be necessary to remove the sulphadiazine from the plasma.⁷

In summary, HIV infection should be considered in patients over 50 years with CNS lesions especially when single or multiple ring-enhancing lesions are present. Clinicians need to be aware of the propensity of sulphadiazine to crystallise in the urine with resultant renal impairment and potential urological morbidity. Proactive hydration, urinary alkalinisation and/or cessation of sulphadiazine may be necessary to preserve kidney function in patients who show signs of crystallisation and/or frank nephrolithiasis.

Learning points

- ▶ A high index of suspicion for HIV infection, AIDS symptoms and indicator conditions such as cerebral toxoplasmosis must be maintained in older patients perceived at lower risk epidemiologically where the diagnosis may be commonly missed.
- ▶ A normal absolute lymphocyte count does not exclude the diagnosis of HIV.
- ▶ Use of sulphadiazine for cerebral toxoplasmosis may be associated with sulphadiazine-induced renal calculi.
- ▶ Aggressive hydration, urinary alkalinisation and/or cessation of sulphadiazine may be necessary to preserve kidney function.

Competing interests None.

Patient consent Obtained.

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