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A 34-Year-Old HIV-Positive Woman from Malawi With Slowly Progressive Half-Sided Weakness

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Clinical Presentation

History

A 34-year-old Malawian woman presents to a neurology outpatient clinic in Malawi with slowly progressive weakness of the left arm and leg.

Her problems started approximately 3 months earlier when she first noticed a limp in her left leg. The weakness progressed, and over the following weeks she also realized that her left arm was becoming affected.

The patient is a poor historian and often has difficulty describing the onset and timing of sequential events, but from her story it appears likely that the problems started insidiously and have been slowly progressing since. She denies any head trauma, headache, recent episodes of fever, nausea, visual impairment or loss of weight. The review of systems is unremarkable.

The patient was diagnosed with smear-positive pulmonary tuberculosis 5 months earlier. At that time, she was also found to be HIV-reactive with a baseline CD4 count of 54/µL. She was started on antituberculous therapy, vitamin B_6, antiretroviral therapy and co-trimoxazole prophylaxis, all of which she is currently taking.

The patient works as a street vendor selling mobile phone vouchers. Despite her left-sided weakness she is still able to work sitting on a plastic chair and managing her vouchers and money with her right hand. She is divorced and does not have any children. She lives in an urban high-density area.

Clinical Findings

She is afebrile and her vital signs and general examination are normal apart from slightly pale conjunctivae. On fundoscopy her fundi are normal without any signs of papilloedema or retinitis.

The neurological examination reveals a spastic hemiparesis on the left with hyperreflexia. The power in the left leg is 2/5 (active movement with gravity eliminated) and in her left arm 3/5 (active movement against gravity). There is a pronator drift on the left (Fig. 51.1) indicating proximal weakness. Sensation of pain is reduced in her left leg and hand. The examination of her cranial nerves is normal.

Laboratory Results

Full blood count: WBC 3.8×10^9/L (reference range: 4–10), haemoglobin 9.9 g/dL (12–14), platelets 140×10^9/L (150–350).

Questions

1. What is your differential diagnosis?
2. What is your diagnostic approach in a resource-limited setting?

Discussion

A 34-year-old HIV-positive woman from Malawi presents with a 3-month history of progressive left-sided weakness of insidious onset. She was diagnosed with pulmonary

• **Fig. 51.1** Pronator drift on the left side as a sign of left upper limb weakness. The patient was asked to stretch out both arms and close her eyes.

tuberculosis (TB) and HIV 5 months before her presentation. She is on antiretroviral therapy (ART), co-trimoxazole prophylaxis and on antituberculous medication. On examination, there is a spastic hemiparesis on the left side with sensory involvement.

Answer to Question 1

What is Your Differential Diagnosis?

The combination of spastic hemiparesis with hyperreflexia and sensory impairment affecting one half of the body localizes the lesion to her brain. The onset appears subactute and the progression is slow. This makes ischaemic and haemorrhagic lesions ('strokes') unlikely causes because they present (hyper-)acutely and usually do not progress. Most likely the patient has one or several focal brain lesion(s).

The differential diagnosis of focal brain lesions (FBLs) in HIV-infected individuals in tropical countries is broad. Patients may suffer from HIV-related brain diseases such as cerebral toxoplasmosis, progressive multifocal leukoencephalopathy, CNS lymphoma, cryptococcoma and CMV encephalitis. *Mycobacterium tuberculosis* infection of the brain parenchyma can present as tuberculoma or tuberculous abscess.

Furthermore, HIV-positive individuals may suffer from conditions primarily unrelated to their HIV infection such as a brain tumour, brain metastases or a cerebral abscess.

Endemic 'tropical' diseases such as neurocysticercosis, neuroschistosomiasis or, in Latin America, Chagas' disease, can also present with focal brain lesions and should be considered according to the local epidemiological pattern.

In this particular case, the patient developed a focal brain lesion 2 months after starting ART. Central nervous system disorders are common after ART initiation. It is thought that the recovering immune system may 'unmask' or 'paradoxically deteriorate' pre-existing CNS infections. This phenomenon is called immune reconstitution inflammatory syndrome (IRIS) and, depending on the type, is termed 'unmasking' or 'paradoxical' IRIS.

Tuberculoma, progressive multifocal leukoencephalopathy (PML) and cryptococcoma have been well documented in the context of IRIS. Toxoplasmosis has been described after ART initiation, even in patients on co-trimoxazole prophylaxis.

Of note, our patient was diagnosed with TB at the time of ART initiation and CNS tuberculosis can deteriorate after ART introduction as well as after commencement of TB treatment.

Answer to Question 2

What is Your Diagnostic Approach in a Resource-Limited Setting?

The diagnostic work-up of FBLs in a resource-limited setting primarily depends on the availability of investigations. It often remains mainly clinical, guided by epidemiological evidence and by the degree of immunosuppression in HIV-positive patients. Clinicians may often find themselves restricted to the pragmatic approach of 'treating the treatable'.

If the patient is HIV-positive, a CD4 count should be performed. Some FBLs are very unlikely if the CD4 count is above 200/μL, e.g. cryptococcoma or cerebral toxoplasmosis. Cerebral TB can occur at any CD4 count. PML mostly manifests in patients with advanced immunosuppression but has also been described in patients with higher CD4 counts.

Serum antitoxoplasma IgG and cryptococcal antigen (CrAG) are helpful, but may not be routinely available. Negative antitoxoplasma serology makes toxoplasmosis a very unlikely diagnosis, whereas a positive serological result documents past contact with the pathogen but fails to prove its relevance for the current illness.

Sensitivity of CSF examination in FBL is low, and both cryptococcoma and tuberculoma may present with a normal CSF. However, if XPert MTB/RIF or Ziehl-Neelsen stain, CrAg, India Ink or fungal cultures are available, these tests should be done and might help establish the diagnosis.

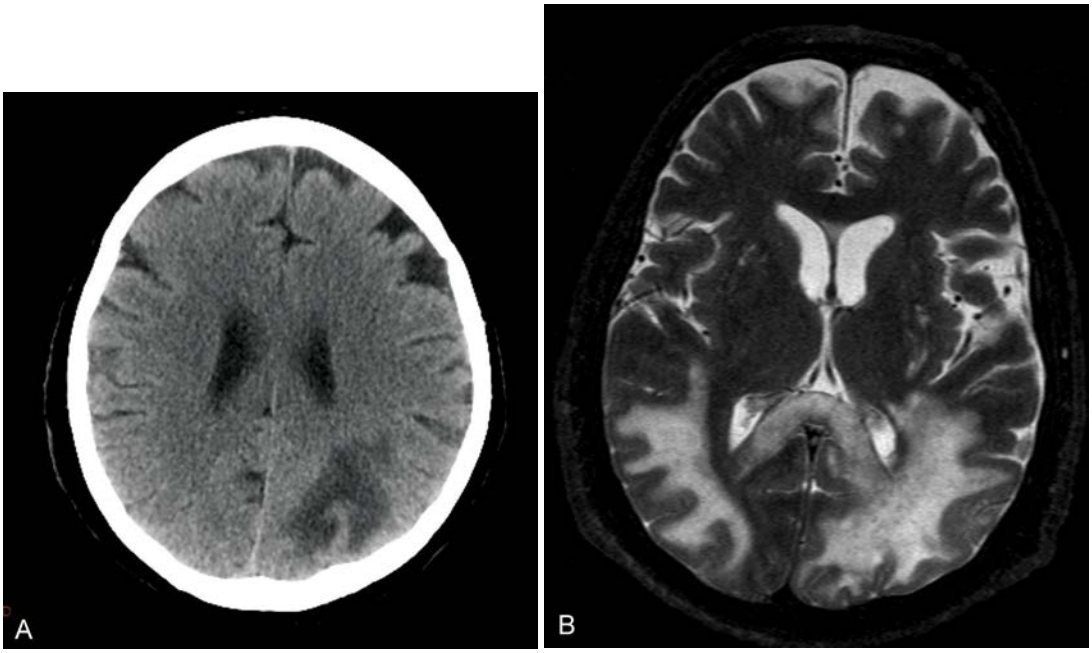
Chest radiography and abdominal ultrasound are useful because they may reveal tuberculous lesions, metastases or a primary neoplasm.

Cerebral imaging plays an important role in diagnosing FBLs; however, availability is extremely limited in resource-constrained settings. CT may at times produce non-specific results confirming the clinical diagnosis of an FBL but failing to assist the clinician in narrowing down the spectrum of differential diagnoses. MRI is more informative; however, it is practically unavailable as a routine investigation in tropical low- and middle-income settings. Cystic lesions on CT are indicative of neurocysticercosis. Cerebral oedema with mass effect and contrast enhancement would favour cerebral abscess, tuberculoma, toxoplasmosis and CNS lymphoma, whereas PML classically shows no mass effect and no enhancement. Meningeal enhancement is typical for tuberculosis.

The Case Continued…

Routine CSF examination was normal, India Ink stain and fungal cultures were negative. The patient was started on empirical antitoxoplasmosis treatment with high-dose co-trimoxazole. ART and antituberculous treatment were continued. Prednisolone 1 mg/kg bodyweight was added to cover for presumed IRIS. The patient was put on a waiting list for a cerebral MRI scan, which was available thanks to a local research project.

On 4-week follow-up her clinical status was unchanged. At 8 weeks there was further deterioration of power in her left hand. An MRI of her head was done which showed multifocal T2 hyperintense lesions exclusively affecting the white matter and more prominent in the right hemisphere (frontal and temporal lobes). Furthermore, there was a small area of demyelination in the left cerebellar peduncle. These radiological findings were deemed strongly suggestive of PML.



• **Fig. 51.2** (A) Cranial CT scan showing a hypodense lesion in the subcortical white matter in the left occipital lobe. (B) Cranial MRI showing bilateral T2 hyperintense (to grey matter) lesions in the subcortical white matter involving the so-called U-fibres resulting in a "scalloped appearance". (Courtesy Dr Eberhard Siebert, University Medical Center Charitè, Berlin, Germany)

A presumed diagnosis of PML was made. The patient was referred to a local rehabilitation centre for walking aids. The local palliative care team was involved.

SUMMARY BOX

Progressive Multifocal Leukoencephalopathy

PML is caused by a reactivation of the human JC polyomavirus. JC stands for 'John Cunningham', the first patient from whom the virus was isolated. JC polyomavirus is neurotropic, affecting oligodendrocytes.

PML always occurs as a result of virus reactivation because of immunosuppression. Primary infection usually takes place during childhood and the virus remains quiescent in the kidneys, bone marrow and lymphoid tissue. Upon reactivation, a productive infection of brain oligodendrocytes results in demyelination. The presenting symptoms include muscle weakness, sensory deficits, hemianopia, cognitive dysfunction, aphasia, and coordination and gait difficulties.

On imaging, multiple lesions are located in the subcortical white matter and cerebellar peduncles. The lesions look hypodense on CT (Fig. 51.2A), and hyperintense on T2-weighted MRI (Fig. 51.2B). There is no mass effect or contrast enhancement.

Besides its importance as an opportunistic infection in advanced HIV infection, PML in recent years has increasingly been described in other contexts of immunosuppression e.g. in transplant patients or patients treated with immunemodulatory drugs.

The only treatment showing benefit in PML patients with HIV is ART. Prognosis before introduction of ART was poor, and only 10% of PML patients survived for 1 year. However, in the ART era the 1-year survival rate has increased dramatically to 50%.

PML occurring within the first months of ART is often described as PML–immune reconstitution inflammatory syndrome (PML–IRIS). Of note, PML–IRIS possibly accounts for nearly 25% of all PML cases in HIV-positive patients. Steroids might have a beneficial effect in the management of PML–IRIS. However, in a setting with high prevalence of HIV-associated opportunistic infections and tuberculosis, it is probably advisable to apply steroids only if other common CNS infections are excluded or covered for.

Further Reading

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