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LETTER TO THE EDITOR

Ophelia syndrome followed by tubercular meningitis in a patient with relapsed Hodgkin lymphoma, could MR imaging have saved his life?

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Introduction

Ophelia syndrome is described in a patient with Hodgkin lymphoma (HL) having neurological symptoms secondary to paraneoplastic limbic encephalitis (PLE). This is associated with antibodies to mGluR5, which may or may not be positive. We report a case of PLE in a relapsed case of HL. The improvement of neurological symptoms and disappearance of brain parenchymal imaging features following chemotherapy was the key diagnostic feature in our case. An unexpected deterioration in the patient's condition resulted from tubercular meningitis 1 month after chemotherapy. The symptoms of neuroinfections may be vague or overlap with other differentials at the outset, and preliminary cross-sectional imaging, such as a non-contrast CT, may be normal. Early diagnosis is very important, especially in immunocompromised individuals, where the chance of death and morbidity is very high. The risk of tuberculous meningitis (TBM) increases in those with a compromised immune system. Cancer patients are at risk of opportunistic infections because of immunosuppression caused by chemotherapy drugs.

Whether the worsening of our patient's condition could have been prevented with an early MRI examination is still a matter of discussion among us. Despite being treated with medications, the patient died after 2 weeks of symptom onset.

Case history

A 40-year-old man was diagnosed to have classical HL stage II in 2017. As there was complete response to the treatment on PET CT after 2 months of chemotherapy, he continued to receive the complete course of six cycles of Adriamycin, Bleomycin, Vinblastine and Dacarbazine chemotherapy. In 2020, he presented with fever for which PET CT was performed, showed interval development of mediastinal and retroperitoneal fluoro-deoxy glucose (FDG) active lymph nodes with splenic deposits. Biopsy from the splenic deposit confirmed relapsed Hodgkin lymphoma. Patient refused further treatment and defaulted. After a year, he presented with persistent fever and fatigability. PET CT scan was repeated for disease assessment and it showed interval increase in the retroperitoneal lymphadenopathy and splenic lesions with new hepatic and skeletal lesions (Fig. 1A, B). During this period, he developed headache, mood and behavioral disturbances for which MRI of brain plain study was advised. It revealed symmetrical diffusion weighted imaging (DWI) bright signal in both the medial temporal lobes and basis pontis and corresponding fluid-attenuated inversion recovery (FLAIR) hyperintensities (Fig. 1C, D). Possible diagnosis of paraneoplastic limbic encephalitis (PLE) was made based on imaging.

Paraneoplastic neuronal antibody workup for PLE was done by redirecting the serum samples to a higher dedicated center. Onconeuronal antibodies including Anti-Hu, Anti-Ri, Anti-Yo, Anti-CV-2, Anti-PNMA2, Anti-amphiphysin, Anti-SOX1, Anti-Tr, Anti GAD65, Anti Zic4, Anti-titin and Anti-Recoverin were negative. However, anti-mGluR5 could not be tested as it was not available in our commercial panel. Differential diagnosis of herpes simplex virus encephalitis was ruled out as cerebrospinal fluid polymerase chain reaction (CSF PCR) testing was negative and there was no involvement of the basifrontal lobes or insula. No test was sent to rule out tuberculosis (TB) at this stage as the imaging

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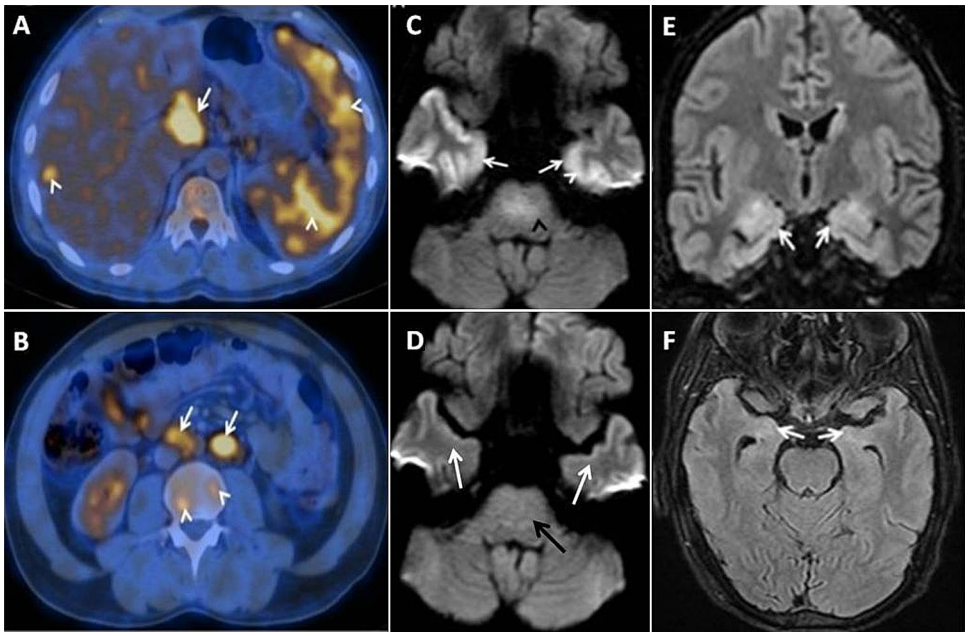

Fig. 1 PET CT showing disease in retroperitoneum, liver, spleen and vertebra (**A**, **B**). MRI before and after chemotherapy in Ophelia syndrome (**C**, **D**, **E**, **F**)

findings were not specific for the disease and no history of TB in the past. Patient received Brentuximab following which neurological symptoms improved dramatically.

Brain lesions resolved following the treatment. This was confirmed on repeat MRI brain plain study which revealed resolution of bright signals on DWI and FLAIR (Fig. 1E, F). There was good partial response to the chemotherapy which showed significant reduction in the size of the liver lesions and retroperitoneal lymph nodes. Patient was discharged with advice of few more cycles of chemotherapy and Brentuximab with an option of autologous stem cell transplant in future.

After a month, patient complained of intermittent headache which was not localized to any particular location. No other symptoms were present. Clinically, there were no positive meningeal signs. As an initial workup, non-contrast CT was performed which did not reveal any abnormality (Fig. 2A). He was treated on outpatient department basis and analgesics were prescribed. Patient returned to emergency department with worsening of headache and restlessness after 5 days. On examination, patient was very restless, not obeying commands and was only responding to the pain stimulus. His complete blood count, liver and renal function tests, urine examination, and TSH were normal. COVID test was negative for SARS-CoV2. Low serum sodium, potassium and chloride were detected for which he was given correction. MRI was advised which showed basal cisternal and bilateral basal ganglial hyperintensity on FLAIR with diffusion restriction and also hydrocephalus (Fig. 2B–F). Imaging diagnosis of TBM was made following contrast MRI. CSF analysis performed and diagnosis of tuberculosis was confirmed (Table 1). He was started on antitubercular treatment. Patient deteriorated rapidly, developed obstructed hydrocephalus. Shunt was placed for hydrocephalus. However, he further worsened clinically, was comatose and expired within the next 5 days.

Discussion

Limbic encephalitis may be infective, autoimmune, or paraneoplastic presenting with symptoms of cognitive dysfunction, mood and behavioral changes, hallucinations, or short-term memory loss. Paraneoplastic variety is seen in solid malignant tumors as well as in hematological malignancies such as lymphomas. PLE in HL has been described in both adults and children and is popularly known as Ophelia syndrome [1]. Anti-mGluR5, a cell surface antibody, is more commonly seen in young adults with Ophelia syndrome. Immunotherapy and underlying cancer treatment have been shown to improve the recovery of patients with mGluR5 antibodies [2, 3]. However, mGluR5 antibody has not been included in most of the commercial panel centers in developing countries as in our case.

Our patient had a relapse of HL affecting extra nodal sites after which he presented with neurological manifestations.

Imaging characteristics of PLE show typical T2/FLAIR hyperintense unilateral or bilateral medial temporal lobes involving the hippocampus and amygdala with or without diffusion restriction/contrast enhancement. Serial MRI may become normal following treatment or may show the progression of the ongoing inflammatory process with the development of hippocampal atrophy and mesial temporal sclerosis. The most important imaging differential diagnosis

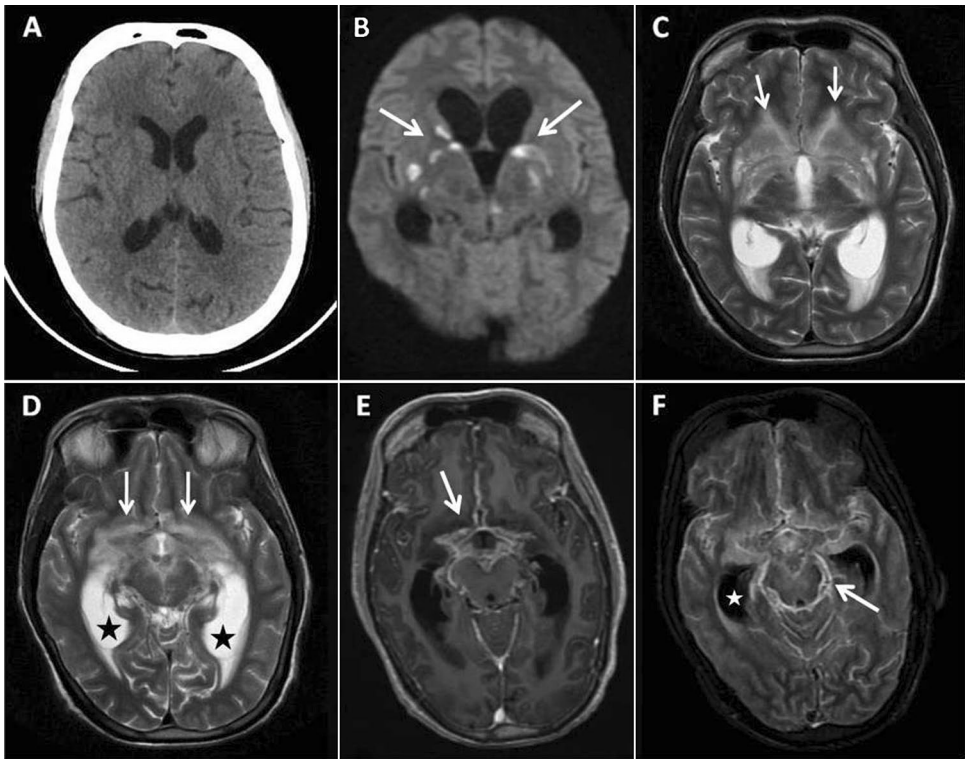

Fig. 2 Normal CT brain (**A**). MRI showing basal ganglia infarcts, hydrocephalus and basal meningitis (**B**, **C**, **D**, **E**, **F**)

is the herpes simplex virus encephalitis. Serological testing and CSF PCR would rule out the cause.

Management of the underlying malignancy improves the condition dramatically. Apart from chemotherapy, immunosuppression, intravenous immunoglobulins, and plasma exchange are also being used.

Though Ophelia syndrome is not an unknown entity in HL, our case of HL was completely cured of his neurological signs and symptoms following chemotherapy, but, the immunocompromised status of the patient due to chemotherapy caused tubercular meningitis in a short interval and was not detected on baseline CT.

In patients with malignancies including both solid organ and hematological ones, the most common cause of death is due to infection as there will be significant immune suppression secondary to chemotherapy and malignant process affecting the host defense mechanisms. Tuberculosis is one of the commonest opportunistic infections in India and accounts for the highest TB burden in the world. It is the most common cause of death in acquired immunodeficiency virus-infected patients. Though there have been continuous efforts to get rid of TB in the country like the launch of National TB elimination program in 2020 and articles on how to improve engaging the private health sector in managing TB, it still poses a serious concern [4–7]. Other opportunistic infections are cytomegaloviral, candidiasis, aspergillosis, herpes zoster, cryptococcosis, toxoplasmosis, etc. Prophylaxis against a few of the organisms may prevent or reduce the opportunistic infections in turn reducing the mortality [8].

Early diagnosis of neuroinfection is very much essential, especially in vulnerable patients. CT may not show any features and is less sensitive than MRI. In patients with immunosuppression or immunocompromise who complain of vague symptoms like headache, the initial modality should ideally be a contrast-enhanced MRI despite no fever which we missed to do so. Contrast-enhanced FLAIR is very sensitive to meningitis. TBM is commonly seen in immunosuppressed/immunocompromised patients. Immunosuppression is seen in old age, following intake of a few drugs such as steroids, chemotherapy, medical illness, and due to malnutrition. Early symptoms of TBM may be very subtle like headache with or without low-grade fever. CT may not show any abnormality. In TBM, basal cisternal spaces show hyperintensity on delayed post-contrast T1 and post-contrast FLAIR suggesting basal meningitis [9, 10]. There may be complications such as hydrocephalus and vasculitis resulting in infarcts as in our case showing basal ganglial infarcts, tubercular abscess formation, or focal cerebritis seen as subtle T2 and FLAIR gyral hyperintensity with or without enhancement. Confirmation of the organism is by CSF analysis and GeneXpert. The drug of choice is antitubercular medications. The opinion that the antitubercular drug could have saved him if it was started a little earlier remains a query.

Table 1 CSF analysis, growth and GeneXpert

Investigations	Results
Glucose	Low (31 mg/dl)
Protein	High (194 mg/dl)
White blood cell count	High (47 cells/cu.mm)
Lymphocytes	90%
Neutrophils	10%
AFB	Negative for acid fast bacilli
KOH mount	Negative for fungal filaments
India ink preparation	Negative for capsulated organisms
Culture and sensitivity	
Gram stain	Moderate pus cells. No bacteria
Growth of organisms	No growth in culture
Meningitis–encephalitis panel	
Escherichia coli K1	Not detected
Haemophilus influenzae	Not detected
Listeria monocytogenes	Not detected
Neisseria meningitidis	Not detected
Streptococcus agalactiae	Not detected
Streptococcus pneumoniae	Not detected
Cytomegalovirus	Not detected
Enterovirus	Not detected
Herpes simplex virus 1	Not detected
Herpes simplex virus 2	Not detected
Human herpes virus 6	Not detected
Human parechovirus	Not detected
Varicella zoster virus	Not detected
Cryptococcus neoformans/gattii	Not detected
GeneXpert	
Mycobacterium tuberculosis complex	Detected
Rifampicin resistance	Not detected

In conclusion, PLE should be suspected when HL patients present with neurological symptoms that are completely reversible by treating the primary malignancy. However, treating cancers result in immunocompromised status which predisposes to infections. MRI has high sensitivity than CT in detecting neuroinfections. Aggressive management in the early setting is very crucial for saving the life of such patients.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution.

Informed consent Informed consent for the patient included in the case report was obtained from the patient's wife as the patient's condition was not stable.

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