Oncology imaging: Diagnosis

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We congratulate Drs Vanesha Naidu of King Edward VIII Hospital, Durban, and Ayesha Mitha of Inkosi Albert Luthuli Central Hospital, Durban, for their excellent diagnoses, for which they share the award of R1 000 from the RSSA. Drs Misser *et al.* elaborate below on the images and findings. Please refer to pages 74 - 76 of the June 2013 issue of the *SAJR* (http://www.sajr.org.za/index.php/sajr/article/view/890/724) for the presenting details (recent onset personality change, depression and cognitive impairment) and the investigative images.

Diagnosis

Imaging and findings

The current imaging undertaken for new-onset neurological symptoms is superimposed on a background of long-standing neoplastic disease. The clinical context in this patient is therefore of great importance to the diagnosis.

The brain MR images (Figs 1 - 3) demonstrate abnormal increased T2-weighted and flair hyperintensity in the medial temporal lobes, particularly on the left side, including the hippocampal formation and amygdala. There is corresponding subtle T1-weighted shortening in the left limbic structures but no significant post-gadolinium enhancement (Fig. 4), which favours an inflammatory/encephalitic process over neoplastic/metastatic disease.

His prior imaging studies (Figs 5 - 13) show extensive intra-abdominal lymphadenopathy, predominantly involving retroperitoneal (para-aortic, interaortocaval, paracaval) and juxtarenal groups. All nodal masses demonstrate restricted diffusion on the diffusion B1000 study (Fig. 10) and corresponding ADC shortening (Fig. 11).

There is evidence for metastatic disease including:

- right lung base nodular parenchymal deposit (Fig. 8)
- left pleural effusion and sub-pleural nodular metastasis (Fig. 12)
- bony metastases to the thoracolumbar vertebral bodies D11, L1 and L2 (Figs 5 - 7)
- hepatic parenchymal lesions in both lobes (Figs 9 - 13).

Hepatocyte-specific contrast MRI shows the metastatic lesions as hypo-intense non-enhancing foci on a background of homogenously enhancing liver parenchyma. Most of them demonstrate restricted diffusion as well. Note the low signal ovoid focus within the lumen of the contrast opacified IVC (Fig. 13) owing to intracaval tumour invasion.

The combination of distant haematogenous and regional nodal metastases, also seen on the sagittal lumbar spine MRI (Figs 5 - 7), in a young male patient is most probably due to a testicular germ cell tumour. Lymphoma is a plausible differential diagnosis. The current neurological presentation is due to paraneoplastic limbic encephalitis.

The patient was treated with salvage chemotherapy and, on follow-up imaging, the nodal masses were noted to be much smaller, the hepatic metastases had cleared completely, the limbic encephalitis changes had resolved, and there was normalisation of tumour markers. At relook laparotomy, the remaining para-aortic nodes were noted to be irresectable. His future management will depend on monitoring of the tumour markers. If there is a rapid elevation in levels, then chemotherapy will be re-introduced. If there is a gradual increase, localised small fields of radiotherapy will be applied to the residual metastatic nodes.

Discussion

Paraneoplastic syndromes are rarely encountered in clinical practice. The relationship between tumours and distant organ symptomatology not attributable to direct tumour effect or metastasis has been described over a century ago. These syndromes represent a distant manifestation of neoplasia on an auto-immune basis. The paramalignant syndromes are divided into paraneoplastic neurological syndromes (PNS) and non-neurological syndromes. Here we will focus on PNS as it is relevant to the patient presented. The pathophysiology of PNS is complex (Fig. 1 in this diagnosis).

During early neoplasm development, apoptotic cells become phagocytosed by dendritic cells and are transported to lymph node stations. There, the dendritic cells induce a cascade of humoral and cell-mediated responses including the activation of T-lymphocytes and B-cells. The B-cells mature into plasma cells and produce antibodies against a tumour-specific antigen in an attempt to destroy it. There are, however, instances where the cytotoxic T-lymphocytes and antibodies produced by the body cross-react with normal tissues and destroy them. Depending on the auto-antibody formed, immune cross-reactivity occurs with destruction of normal tissue, and symptoms relevant to that organ system will manifest. In PNS, one of the components of the nervous system (Table 1) will be involved owing to immune cross-reactivity by the produced onco-neural antibodies. Fig. 1 describes the combined auto-immune response resulting in destruction of neuromuscular junction in the Lambert-Eaton myaesthenic syndrome. The same principle applies to the other PNS subtypes.

An increasing number of onconeural antibodies have been identified in patients with PNS, including anti-Hu, anti-CV2, anti-Ma and anti-Ta (Ma2), among several others.[1] Anti-Ta (Ma2) typically occurs in young men with testicular germ cell tumours (including extragonadal sites). Paraneoplastic limbic encephalitis (PNLE) was first described

Table 1. Location of paraneoplastic neurological syndrome and subtypes described

Brain	Limbic encephalitis Brainstem encephalitis Cerebellar degeneration Opsoclonus-myoclonus Visual syndromes – cancer-associated retinopathy, optic neuritis Extrapyramidal syndromes – chorea, parkinsonism
Spinal cord	Necrotising myelopathy Inflammatory myelitis Motor neuron disease Stiff person syndrome Subacute motor neuropathy
Dorsal root ganglion	Sensory neuropathy
Peripheral nerve	Autonomic neuropathy Acute sensorimotor neuropathy, e.g. Guillain-Barré syndrome Chronic sensorimotor neuropathy Vasculitic neuropathy Neuromyotonia
Neuromuscular junction	Lambert-Eaton myaesthenic syndrome Myaesthenia gravis
Muscle	Polymyositis/dermatomyositis Necrotising myopathy Myotonia

Table 2. Criteria for diagnosis of PLE[3]

Compatible clinical picture

Interval of <4 years between diagnosis of tumour and presentation with PLE

Exclusion of other neuro-oncological complications

At least 1 of the following:
- CSF with inflammatory changes but negative cytology
- Characteristic temporal lobe MRI abnormalities
- EEG demonstrating epileptic activity in temporal lobe

by Corsellis *et al.*[2] in 1968. Patients with PNLE may present with subacute personality change, major depression, irritability, amnesia and convulsions. Some patients can progress to dementia.

The diagnosis of PNLE depends on several related criteria, as outlined in Table 2. Radiological imaging by MRI has become an integral component in making this profound clinical diagnosis. On flair and T2-weighted imaging, abnormal shortening resulting in hyperintensity is usually documented in the temporobasal regions, especially the limbic structures including the hippocampus and amygdala. The main differential diagnosis for these MRI changes is herpes simplex encephalitis, the presentation of which is more acute. In many instances, the flair sequence may be the only contributory sequence depicting the medial temporal lobe abnormality. Gultekin

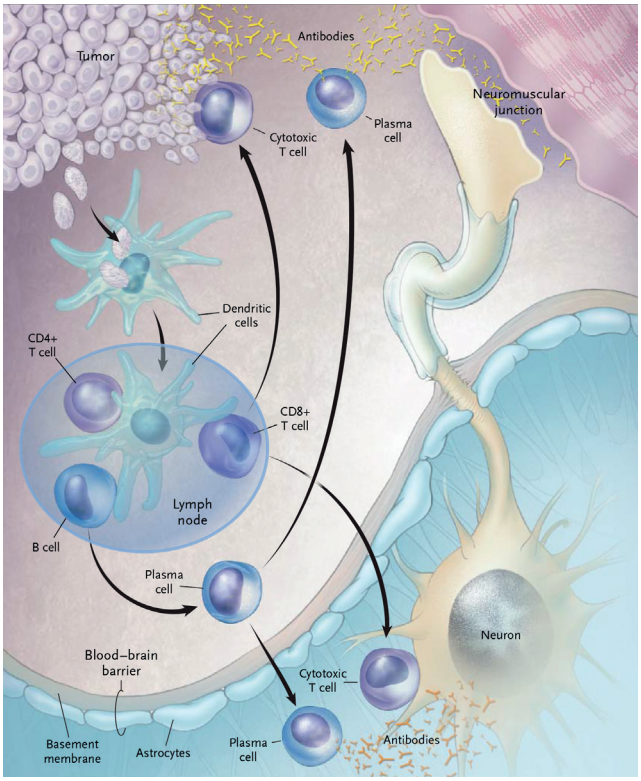

Fig. 1. Pathophysiology of PNS with activated CD-8 lymphocyte and plasma cell induced cell-mediated and humoral immune reaction to neural tissue resulting in target organ damage. (Reproduced with kind permission of Dr J B Posner.)

et al.[3] showed absence of T2-weighted abnormalities in 43% of their series of patients. Corresponding T1-weighted low signal may be seen and post-gadolinium enhancement is generally absent. Isolated cases demonstrating post-contrast T1-weighted enhancement of the limbic structures have been documented. In clinical practice, the radiologist is usually the first to raise the alarm that a paraneoplastic phenomenon is suspected, and correlation with other criteria for PNLE follows.

Generally, these patients respond well to immunotherapy and treatment of the underlying malignancy.[1] Follow-up imaging to document clearing of the medial temporal lobe abnormality is recommended. The radiologist therefore plays a pivotal role in the diagnosis and follow-up of these patients.

1. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. New Engl J Med 2003;349:1543-1554. [http://dx.doi.org/10.1056/NEJMra023009]
2. Corsellis JA, Goldberg GJ, Norton AR. "Limbic Encephalitis" and its association with carcinoma. Brain 1968;91(3):481-496. [http://dx.doi.org/10.1093/brain/91.3.481]
3. Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Damau J. Paraneoplastic limbic encephalitis: Neurological symptoms, immunological findings and tumour association in 50 patients. Brain 2000;123:1481-1494. [http://dx.doi.org/10.1093/brain/123.7.1481]

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