Limbic encephalitis associated with immature teratoma

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Summary

Paraneoplastic neurological syndrome (PNS) includes rare manifestations of different forms of cancer, in which the specific syndrome of limbic encephalitis can be found. This report describes a case of a previously healthy young lady who developed severe limbic encephalitis associated with an immature teratoma. After surgical treatment, the patient showed rapid progressive neurological improvement with complete regression of the symptoms during follow-up. Although rare, correct recognition and management of PNS is of great importance especially considering the fact that PNS can carry the risk of permanent disability or even death, even when associated with tumors in which high cure rates are expected.

Key words: Germ cell; Teratoma; Limbic encephalitis; Ovarian cancer; Paraneoplastic; Neurological syndromes.

Introduction

Paraneoplastic neurological syndrome (PNS) is characterised by signs or symptoms related to tissue damage at sites which are distant from the primary tumor or its metastasis. PNS is not related to metabolic, infectious, ischemic, or nutritional complications nor side-effects from the oncologic therapy [1]. Although some cases have been associated with benign tumours of indolent behaviour, in which high recovery rates are expected, such syndromes may have severe or even fatal outcomes. A severe case of limbic encephalitis associated with an ovarian teratoma is presented together with a brief review of the literature.

Case Report

A previously healthy 32-year-old female presented with a two-month history of abnormal behaviour and anxiety followed by depression, mental confusion, amnesia, and aphasia. The patient was initially treated by a psychiatrist with risperdal. Upon progressive worsening in the psychiatric and neurological states, the patient began to have a convulsive crisis and fever and was subsequently transferred to a tertiary hospital. Empirical treatment with acyclovir was begun due to the suspicion of herpetic encephalitis with no improvement. A magnetic resonance imaging (MRI) brain scan revealed signs of rare abnormality spots in the subcortical white matter and in periventricular frontoparietal convexities. The patient deteriorated into a stupor and coma, thus calling for immediate invasive respiratory support. A pelvic mass on the left side was noted during this period, and pelvic computed tomography (CT) revealed a calcified ovarian mass (Figure 1A). The patient was submitted to total amplified hysterectomy for ovarian cancer. Further anatomical and pathological exams of the ovarian mass revealed a grade 2 immature teratoma (Figure 1B). Since a classic neurological syndrome – limbic encephalitis – and a malignant tumour were both present, the definitive diagnosis of PNS was made. The patient had rapid progressive neurological improvement, and mechanical ventilation was removed on the second postoperative day. A few days later, the patient was discharged from the hospital with discrete short-term memory impairment. Afterwards, she was submitted to adjuvant chemotherapy with the BEP (cisplatin, etoposide, and bleomycin) regimen and then underwent follow-up. Twenty-eight months after surgery the patient remains with no neurological deficits, negative tumour markers as well as no evidence of activity of the disease.

Discussion

Paraneoplastic neurological syndrome (PNS) is a rare manifestation of different forms of cancer, in which the specific syndrome of limbic encephalitis can be found. It is believed that the majority of PNS are immune-mediated, and their pathogeneses are related to the tumour's ectopic expression of an antigen, which is normally expressed exclusively in the nervous system. This antigen is recognised by the immune system as foreign, leading to an abnormal immune response that can attack the nervous system (either by producing antibodies or through cellular response: B- and T-lymphocytes) [1-3].

Normally, neurological abnormalities precede the identification of the tumour. While in some cases the tumour presents indolent behaviour, neurological paraneoplastic-associated disorders may present rapid, severe, disabling, and, in some cases, lethal outcomes. Today many antibodies are recognised as being able to bind specific neurological and tumour targets, representing powerful tools for diagnosis. However, PNS can occur without the presence of an onconeural antibody, or the antibody may be present in the absence of the neurological syndrome; hence, the presence of an antibody is not the only condition that defines a paraneoplastic neurological syndrome [4-6].

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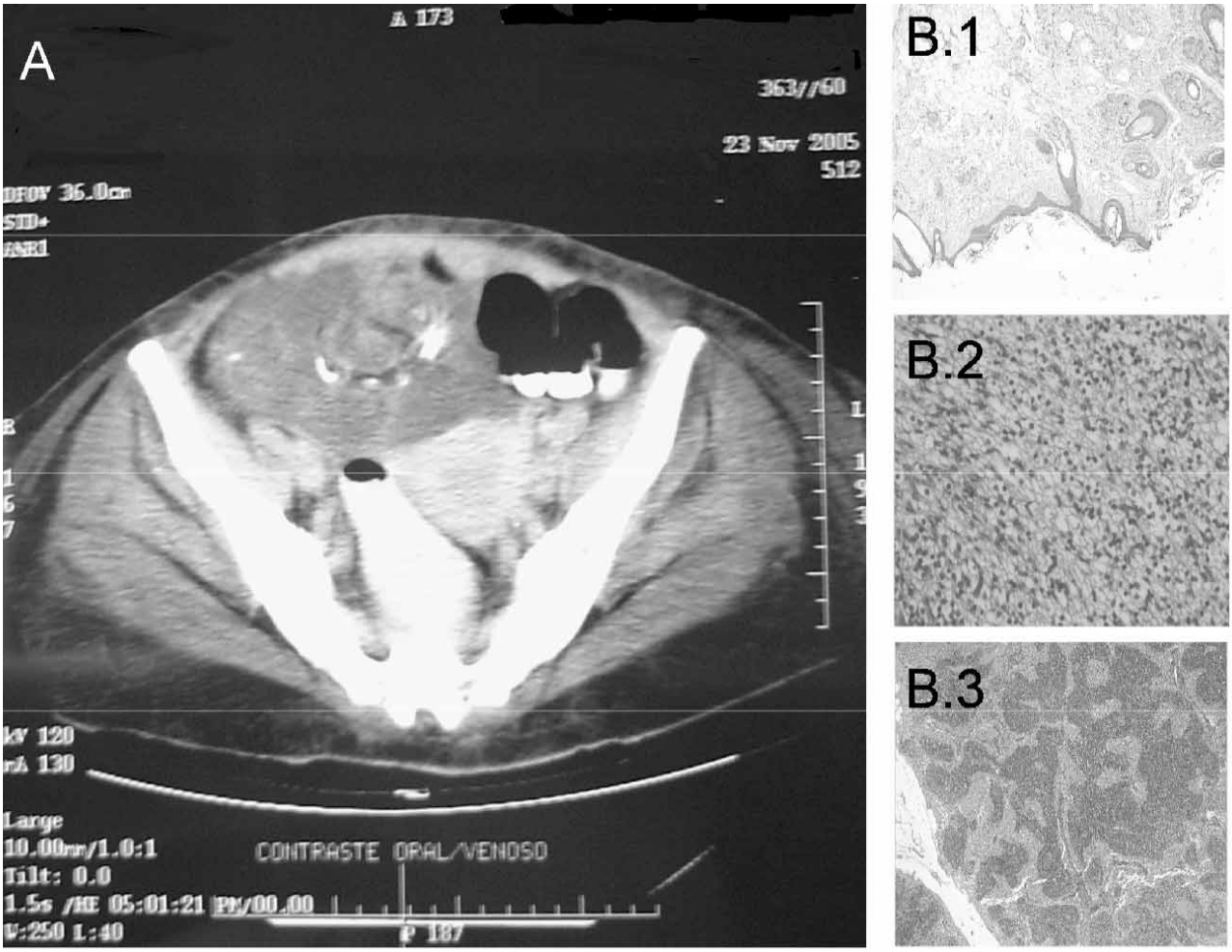

Figure 1. — (A) Computed tomography of the pelvis showing a calcified ovarian mass. (B) Dry tumour section observed: (B.1) Well differentiated area with scaly tissue and skin annexes (H&E 100 X); (B.2) Poorly differentiated area with neural tissue (H&E 400X); (B.3) Mesenchymal areas with bone-cartilage differentiation (H&E 100 X).

Considering their pathogeneses, the treatment of these syndromes is based on two pillars: withdrawing the antigen source through the treatment of the tumour and/or the suppression of the immune response through immunotherapy (e.g., corticosteroids, plasma exchange, intravenous immune globulin, cyclophosphamide, cyclosporine, and tacrolimus). Improvement of neurological symptoms can vary according to the nature of the paraneoplastic syndrome. Usually, in cases in which damage occurs in sites where the nervous system is able to regenerate (e.g., myelin layer, synapses), improvement is expected with treatment. When neurons are destroyed, the treatment can prevent the progression of neurological damage, but regression of the symptoms is rarely observed.

Limbic encephalitis is a classic PNS characterised by a progressive acute or sub-acute change in behaviour, mood, cognitive dysfunctions, hallucinations, and partially-complex convulsive crises. The selective loss of recent memory is a common alteration [7, 8]. Hypothalamic dysfunction leading to hyperthermia, somnolence, and endocrine abnormalities may also occur. Ventilation difficulties have been reported (central hypoventilation) [9]. Fluid exams show inflammatory alterations in up to 80% of the cases and alterations in nuclear MRI or CT can be found in 65-80% of the cases. Electroencephalographic findings include focal or generalised slowing, and occasionally epileptic activity, mostly in the temporal areas [1].

Symptoms of limbic encephalitis can also be found in other diseases, such as viral encephalitis (especially herpes simplex), systemic lupus erythematosus, Wernicke-Korsakoff encephalopathy, toxic effects of doxifluridine, and non-paraneoplastic limbic encephalopathy related to voltage-gated potassium channels [10, 11].

The most frequent tumours associated with this syndrome are lung cancer (especially small cell lung cancer (SCLC)), testicular cancer, thymoma, breast cancer, Hodgkin's lymphoma, and immature teratoma. Antineuronal autoantibodies can also be found in up to 60% of the cases, including anti-Hu (normally related to SCLC),

anti-Ma2 (associated to testicular cancer), anti-Ma1, anti-CV2/CRMP5 (thymoma and SCLC), and anti-VGKC (thymoma and non-paraneoplastic limbic encephalitis), which is the most common [1].

The majority of patients with paraneoplastic limbic encephalitis do not respond well to treatment, although in some cases improvement of symptoms can occur (usually associated with primary tumour treatment and, rarely, with spontaneous resolution).

Conclusion

Ovarian germinative tumours are relatively rare, constituting 2% to 3% of all ovarian cancers. These tumours typically affect children and young women and present high cure rates. Immature teratomas are responsible for 10% to 20% of ovarian tumours found in women under 20 years of age, representing the second most common germinative cell tumour [12]. Patients with Stage I and histological grade 1 present a 5-year survival rate of 90% with surgical treatment. Although there are still controversies, adjuvant chemotherapy with BEP is recommended after surgery for patients with histological grades of 2 to 3 (Stage I) or Stages II to IV. A long-term survival rate of 75% to 80% is expected even in cases of diseases at advanced stages with incomplete resection [12, 13].

The present case study shows a previously healthy young patient, carrier of a tumour with a high rate of cure, and yet her paraneoplastic neurological conditions were considered severe, almost fatal. After appropriate treatment, regression of the symptoms could be observed, and the patient is now living a normal life with no symptoms at all. Although rare, it is important both for the oncologist as well as for the gynaecologist to clearly recognise PNS symptoms. Because of the risk of permanent neurological disability, a specific oncologic treatment or immunosuppressive therapy (even in the absence of a diagnosis of cancer) should not be delayed [14].

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