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CORRESPONDENCE

Paraneoplastic cerebellar degeneration and endometrial cancer: a rare occurrence

Sir,

Paraneoplastic syndromes, the remote effects of cancer, can affect several organs; paraneoplastic neurological syndromes (PNS) are rare, occurring in <1% of cancer patients.[1] They are often associated with antibodies against neural antigens expressed by the tumour, and thus are immune mediated.[1] PNS include several different entities like limbic encephalitis, subacute sensory neuronopathy, opsoclonus-myoclonus, Lambert–Eaton myasthenic syndrome, paraneoplastic peripheral nerve hyperexcitability and paraneoplastic cerebellar degeneration (PCD).[1] PCD is usually associated with breast and ovarian cancer, small cell lung carcinoma and Hodgkin's lymphoma.[1]

We report a case of PCD in a patient with a grade 3 endometrioid endometrial carcinoma diagnosed by presence of serum anti-Yo antibodies, but also confirmed by the immunofluorescence positivity of the tumour for anti-Yo antibodies.

A 74-year-old woman, with a medical history of a surgically treated breast cancer 15 years ago, presented with dysarthria and ataxia and progressive worsening of her symptoms over the previous 3 months. She also noticed postmenopausal bleeding. Magnetic resonance imaging (MRI) revealed a 10 cm uterine tumour and hysteroscopic curettage showed a high-grade carcinoma. No metastatic CNS disease was found, nor evidence of breast cancer relapse. Anti-Yo antibodies were detected in the serum. Total hysterectomy with bilateral adnexectomy, omentectomy and pelvic/aortic lymph node excision were performed.

Pathological examination revealed a high-grade carcinoma of pT1aN2 stage, with vascular invasion. The ovaries were atrophic with no tumour involvement. The tumour was composed of cohesive cells forming solid sheets with marked atypia, occasionally with the form of giant 'monster' cells (Fig. 1A,B), which were negative for βHCG, desmin and myogenin. Focally, residual glandular lumens of endometrioid morphology were found inside the solid foci (Fig. 2A). An infrequent finding was noted: a dense plasma cell and moderate lymphocytic infiltrate (Fig. 1B and 2). Immunohistochemically, the tumour uniformly strongly and diffusely expressed pan-keratins, CK18, EMA and Vimentin (Fig. 1C). Hormonal receptors were not expressed. p53 showed a normal (weak and focal) expression (Fig. 2B). Immunohistochemical staining for DNA MMR proteins (MLH1, PMS2, MSH2 and MSH6) showed no loss of expression. These features prompt a differential diagnosis of serous versus grade 3 endometrioid carcinoma, with the normal expression of p53 being in favour of an endometrioid carcinoma.

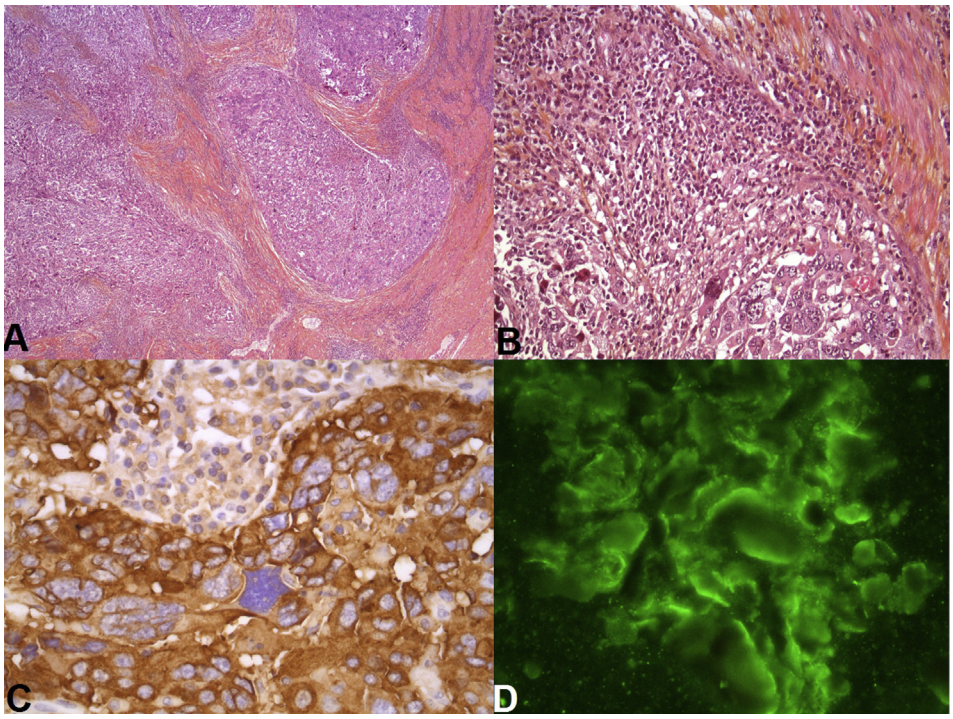

Fig. 1 (A) Microscopic features of the endometrial tumour invading the myometrium (haematoxylin, eosin, saffron; HES). (B) Intense plasmolymphocytic reaction and giant atypical tumour cells (HES). (C) Strong and uniform expression of EMA (DAB). (D) Patient's tumour cryostat section treated with anti-Yo+ serum showing positive reaction (FITC).

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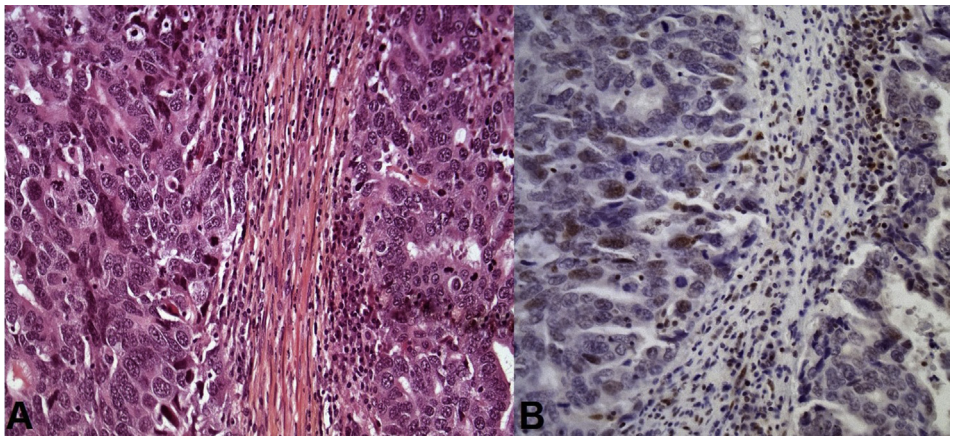

Fig. 2 (A) Rare residual glandular lumens resembling endometrioid carcinoma (haematoxylin, eosin, saffron). (B) Weak and focal (normal) p53 expression (DAB).

Cryostat sections of the tumour and of two other endometrioid carcinomas of patients with no neurological syndrome, serving as controls, were subjected to indirect immunofluorescence (BRIF no. BB-0033-00041). Briefly, cryostat sections of the three uterine tumours were incubated with anti-Yo positive (dilution 1/50) and anti-Yo negative (dilution 1/50) serum for 30 min, followed by washing (PBS) and application for 30 minutes of fluorescein isothiocyanate (FITC)-conjugated anti-IgG. After washing (PBS), coverslips were mounted and the slides were immediately examined under the fluorescence microscope. The current tumour revealed a positive reaction (Fig. 1D), while the two controls were negative. Similarly, anti-Yo negative control serum showed no reaction for any of the three tumours tested.

The patient received adjuvant chemotherapy of carboplatin/taxol/bevacizumab and immunoglobulin therapy. There was neither improvement nor deterioration of the neurological symptoms or cancer recurrence 6 months after initial diagnosis.

Paraneoplastic cerebellar degeneration is characterised clinically by rapidly evolving cerebellar symptoms of nystagmus, dysarthria, and appendicular and gait ataxia, and pathologically by widespread loss of cerebellar Purkinje cells, which in gynecological cancers is caused by the anti-Yo type of antibodies; these result from an immune response to neural antigens expressed by the tumour, but they also cross-react with Purkinje cells.[2] The exact mechanism responsible for Purkinje cell death due to the anti-Yo antibodies is not yet clear, but these antibodies react with the intracellular Yo antigen leading to cell death, not associated with just the intracellular accumulation of the antibody nor the presence of inflammatory cells, but rather the specific binding, suggesting a possible important action of the Yo molecule for Purkinje cell survival.[3]

The neuronal cell destruction explains the stabilisation rather than the clinical improvement of these patients despite treatment, and highlights the need of early intervention to prevent neuronal cell death and irreversible disability.[1] Most cases of PCD show a severe and irreversible syndrome and only rarely is the treatment of the tumour associated with a favourable evolution of the neurological disease.[4] Apart from treating the underlying tumour, immunosuppressive therapy has also been applied, with no significant benefit in most cases.[5] In our case, despite aggressive treatment regarding the tumour and also immunoglobulin administration, no improvement was noted. However, stabilisation of the neurological symptoms was achieved.

Paraneoplastic cerebellar degeneration has been described mostly in women with breast and ovarian cancer and rarely in men or other forms of malignancies. Uterine cancer rarely causes PCD (Table 1).[4–10] In the current case, investigation for possible relapse of the previous breast carcinoma was negative, anti-Yo antibodies were detected in the serum of the patient, but also anti-Yo antibodies reacted with the tumour, confirming the endometrial cause of the syndrome. No such reaction with the tumour has previously been investigated among the cases of endometrial-associated PCD. In a series of 92 patients with PNS and breast or gynecological cancer diagnosed in two reference centres, PCD was the most frequent PNS, followed by sensory neuropathy.[4] Among them three uterine tumours were identified, all with PCD and anti-Yo serum antibodies, but with no information regarding histology of the tumour.[4] In another series of 55 patients with PCD and anti-Yo serum antibodies, four endometrial tumours were found; in one where histology was available, dense lymphoplasmacytic infiltrate was reported.[5] We also noticed an intense plasmolymphocytic reaction at the tumour, a finding we consider part of the disease.

To conclude, we report a rare case of anti-Yo positive paraneoplastic cerebellar degeneration in a patient with uterine cancer, confirming through anti-Yo positive tissue reaction that endometrial tumours can be the cause of this syndrome. We also show that in cases with unusual presentation, detection at the level of the tumour of an anti-Yo reaction by immunofluoresence can be used as an adjunct to the diagnosis of paraneoplastic syndromes.