Lessons from practice

Chorea as a paraneoplastic syndrome heralding the transformation of non-Hodgkin lymphoma

Clinical record

An 81-year-old woman presented with subacute chorea as a paraneoplastic neurological syndrome (PNS) heralding the relapse and transformation of splenic marginal zone lymphoma (SMZL) into diffuse large B cell lymphoma (DLBCL).

The patient was diagnosed with SMZL in 2016. She was treated with rituximab-based chemotherapy, achieving 3 years of complete remission. She relapsed twice before commencing ibrutinib in 2019. The patient reported 6 months of imbalance and left leg paraesthesia with restlessness, slowed cognition, and anxiety. The ibrutinib dose was reduced due to the possibility of neurological side effects. Despite this, she developed left arm involuntary movement, progressing into severe generalised chorea over 2 weeks. She denied use of antiemetics or neuroleptics. No prior or family history of neurodegenerative disorders was reported. Ibrutinib was ceased due to concern about opportunistic infections, including progressive multifocal leukoencephalopathy.

Examination revealed left- greater than right-sided chorea and ballism without cerebellar signs, dystonia, parkinsonism, or apraxia. She demonstrated symmetrically brisk reflexes with stocking-distribution sensory loss to light touch and vibration. She had mild dysarthria without dysphasia. Her Montreal Cognitive Assessment and mental state examination were normal.

Contrast-enhanced magnetic resonance imaging brain and cervical spine scan and nerve conduction study were normal. Negative investigations included biochemical and metabolic panels; coeliac disease antibodies; serologies for cytomegalovirus, human immunodeficiency virus and hepatitis viruses; Huntington disease genetic testing; extractable nuclear antigens; and antinuclear antibody. Autoimmune and paraneoplastic antibody panels were also negative, including antibodies to CV2/collapsin response-mediator protein 5 (CRMP5) and N-methyl-D-aspartate receptor. Cerebrospinal fluid analysis revealed oligoclonal bands and normal biochemistry, microscopy, culture, and flow cytometry. There was no evidence of opportunistic infections, including *Cryptococcus*, BK virus, or JC virus. The 14-3-3 protein was negative, excluding Creutzfeldt–Jakob disease.

Full blood count showed lymphocytosis (40.1 × 10^9/L; range, 1.0–4.0 × 10^9/L) with rapid doubling. Peripheral film showed lymphocytosis comprising pleomorphic lymphocytes with a proportion of large cells with open chromatin. Bone marrow biopsy examination was performed due to suspicion of transformation to DLBCL. Lymphocytes comprised 79% of cells with large lymphocytes seen in the aspirate trails. The trephine biopsy showed an extensive lymphoid infiltrate of large and small lymphoid cells. Flow cytometry confirmed the presence of a monoclonal B cell population (CD5 partial, CD10–, CD19+, CD20 partial, CD23–, with lambda light chain restriction of surface immunoglobulin). Positron emission tomography (PET) scan was negative for fluorodeoxyglucose-avid lymphadenopathy and showed moderately avid splenic uptake consistent with SMZL. These findings, in conjunction with constitutional symptoms and markedly elevated lactate dehydrogenase, were consistent with large cell transformation confined to the marrow.

The chorea responded favourably to clonazepam 0.5 mg twice a day, although she had residual dysarthria and mild chorea. The patient was treated with palliative chemotherapy, which resulted in normalisation of peripheral lymphocytosis and lactate dehydrogenase and complete resolution of chorea and constitutional symptoms. End-of-treatment bone marrow aspirate and trephine biopsy were consistent with remission from DLBCL.

Discussion

We described a patient who developed paraneoplastic chorea in the setting of transformation from SMZL to DLBCL. Histological transformation occurs in 5% of SMZL cases.[1]

While chorea is increasingly recognised as a PNS,[2,3] more common aetiologies of adult onset acquired chorea include drugs (eg, dopaminergic medications, neuroleptics, anticonvulsants, calcium channel blockers); other autoimmune and inflammatory conditions, such as antiphospholipid antibody syndrome and systemic lupus erythematosus; cerebrovascular disease; non-ketotic hyperglycaemia; and central nervous system infection.

Paraneoplastic chorea is most commonly related to solid organ tumours and rarely haematological malignancies.[2,3] Consideration of PNS by the treating clinician can lead to early cancer diagnosis, as PNS precedes tumour identification in 65% of cases.[2] Detection of an autoantibody with predictive value for a specific cancer can narrow the differential for cancer type,[4] but 18.3% of definite PNS do not reveal onconeural antibodies.[2] Almost half of PNS cases are paraneoplastic cerebellar degeneration (24.3%) or sensory neuronopathy (24.3%), and the majority are subacute in onset.[2]

The precise pathogenesis of paraneoplastic autoimmunity and neuronal cytotoxicity is unclear. Specifically in paraneoplastic chorea, it has been suggested that CRMP5 IgG may induce selective

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basal ganglia insult via cytotoxic T cells.[4] Onconeural antibodies directed against intracellular antigens are likely to activate antigen-specific cytotoxic T cells rather than being directly disease-mediating.[5] This theory is supported by animal models demonstrating autoimmune T cell responses in the central nervous system to paraneoplastic autoantigens[6] and by autopsy studies in humans with PNS showing extensive infiltrate of cytotoxic T cells surrounding neurons.[5] Furthermore, the transfer of anti-Hu IgG does not induce clinical disease in animals,[6] nor is there correlation between serum CRMP-5 antibody titre and severity of chorea.[4]

There is often a delay in the diagnosis of seronegative non-classical PNS. Although paraneoplastic chorea is an uncommon PNS, underlying malignancy should always be considered, especially haematological malignancies when investigations for solid organ tumours are negative, in order to facilitate timely investigation and cancer surveillance.

Lessons from practice

- Paraneoplastic neurological syndrome (PNS) presentations are diverse and require a high level of vigilance for their recognition, with serious consequences if missed.
- Paraneoplastic antibodies are not sensitive for PNS.
- PNS can often precede cancer diagnosis. Even if cancer is not identified at the time of presentation, close ongoing surveillance is required.
- Although unusual, movement disorders can be the presenting problem of PNS.

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References are available online.

1 Conconi A, Franceschetti S, Aprile von Hohenstaufen K, et al. Histologic transformation in marginal zone lymphomas. *Ann Oncol* 2015; 26: 2329–2335.

2 Giometto B, Grisold W, Vitaliani R, et al. Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. *Arch Neurol* 2010; 67: 330–335.

3 O'Toole O, Lennon VA, Ahlskog JE, et al. Autoimmune chorea in adults. *Neurology* 2013; 80: 1133–1144.

4 Vernino S, Tuite P, Adler CH, et al. Paraneoplastic chorea associated with CRMP-5 neuronal antibody and lung carcinoma. *Ann Neurol* 2002; 51: 625–630.

5 Dalmau J, Geis C, Graus F. Autoantibodies to synaptic receptors and neuronal cell surface proteins in autoimmune diseases of the central nervous system. *Physiol Rev* 2017; 97: 839–887.

6 Pellkofer H, Schubart AS, Höftberger R, et al. Modelling paraneoplastic CNS disease: T-cells specific for the onconeuronal antigen PNMA1 mediate autoimmune encephalomyelitis in the rat. *Brain* 2004; 127: 1822–1830. ■