Editor's Corner

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Importance of clinical observations

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Clinical case reports can be powerful and informative; they can suggest novel hypotheses, identify gaps of knowledge, and provide suggestions for improvement. In this issue of *Neurology® Neuroimmunology & Neuroinflammation,* Hottinger et al.[1] report a fascinating case with interesting implications. The authors describe a 71-year-old woman with metastatic small-cell lung cancer (SCLC) who developed anti-Hu–associated paraneoplastic encephalitis 4 days after receiving treatment with immune checkpoint inhibitors (nivolumab and ipilimumab). Considering that this disorder is mediated by cytotoxic T cells against a family of onconeuronal antigens (Hu proteins), the authors reasoned that natalizumab would block the migration of onconeuronal-specific T cells across the blood-brain barrier preventing neuronal damage, while not affecting T-cell activity against the systemic cancer. Indeed, after treatment with natalizumab, the patient showed substantial improvement of the neurologic disorder as well as a durable oncologic response. In addition to several interesting points raised by the authors, the case is remarkable for the following reasons: (1) it strongly supports the concept that anti-Hu–associated paraneoplastic symptoms are predominantly mediated by cytotoxic T-cell mechanisms. Although this syndrome develops in association with antibodies that are excellent biomarkers of the paraneoplastic disorder, the underlying (and still not well understood) mechanisms are predominantly dependent on T cells. The most powerful evidence of this comes from autopsy studies demonstrating neuronophagic nodules of T cells along with extensive neuronal loss and glial proliferation.[2] Steroids, plasma exchange, or IV immunoglobulin may partially ameliorate symptoms but rarely stop progression of the disease.[3] These features are in contrast to those of neurologic diseases mediated by antibodies, such as myasthenia gravis or several types of encephalitis associated with antibodies against cell surface proteins[4]; (2) this case and previous reports of patients who developed paraneoplastic syndromes after treatment with immune-mediated checkpoint inhibitors[5] suggest the occurrence of silent or subclinical onconeuronal-specific cytotoxic T cells that can potentially cause severe neurologic dysfunction if unleashed by drugs that restore their cytotoxic potential to attack the cancer. Furthermore, one would expect this complication to be more frequent in patients with neuroendocrine tumors or tumors that express a wide variety of neuronal proteins, such as SCLC; and (3) the observation by Hottinger et al. deserves further investigation and if confirmed, prospective clinical trials assessing natalizumab as a potential treatment of anti-Hu and other similarly devastating paraneoplastic syndromes should be considered.

In another study, Guerrier et al.[6] examined whether changes in subsets of B cells and the profile of cytokine production were distinctly associated with specific stages of MS. A total of 89 patients with MS at different disease stages and 36 healthy participants were included in the study, which examined peripheral blood B-cell subset distributions and the IL6/IL10 ratio assessed by flow cytometry. The authors found that an increase in the IL6/IL10 ratio in patients with radiologically isolated syndrome (RIS) and clinically isolated syndrome (CIS) was significantly associated with disease activity within the following 6 months. This cytokine imbalance resulted from a decrease of IL10-producing B cells rather than an increase of IL6-producing cells, which were unaffected. Alteration in the production of IL10 in patients with RIS or CIS depended predominantly on transitional B cells and was unrelated to type I interferon secretion. These features

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were not identified in the baseline samples of patients with relapsing-remitting MS (RRMS). Finally, the authors did not find alterations in the distribution of B-cell subsets (transitional, mature, naive, and memory) at any phase of the disease, with the exception of the double negative (IgD-/CD27-) B-cell subset, which was overrepresented in patients with CIS and RRMS. These cells are described as exhausted B cells in a chronic activation status but of unclear functional properties. Overall, the findings of this study, which need a replication cohort, suggest that cytokine imbalance at early stages of the disease may assist in identifying those patients who will have disease progression in the ensuing months and will need treatment.

In another study, Bucelli and Pestronk[7] performed a retrospective chart and pathology review of 57 consecutive patients with pathologic findings characterized by damage to perimysial connective tissue and muscle fiber necrosis more prominent near the perimysium. The authors coined the term "immune myopathies with perimysial pathology" (IMPP) to group several known clinical and serological disorders such as inflammatory myopathies occurring with antibodies against aminoacyl–tRNA synthetase or hydroxymethylglutarylCoA reductase. The clinical and pathologic features of this complex group of disorders were then compared with those of 20 patients with dermatomyositis with vascular pathology. Patients with IMPP were more likely to have interstitial lung disease (ILD), Raynaud phenomenon, mechanic's hand, arthralgias, a sustained response to immunotherapy, and less frequently a concurrent cancer. In addition, patients with IMPP more frequently had Jo1 (histidyl-tRNA synthetase) antibodies and SSA/SSA52 antibodies and less frequently antinuclear antibodies. The findings are not surprising, considering the different clinical/serological phenotypes that encompass IMPP, but the authors argue that this pathology also occurs in patients without myositis-associated antibodies, and therefore, its recognition has important clinical implications such as identifying patients at higher risk of ILD. The authors acknowledge that the study is retrospective, spanning a 24-year period, and could not guarantee that diagnostic testing, including myositis-associated antibodies, was uniform across all subjects. Prospective studies with comprehensive pathologic and serological studies are needed to confirm whether this pathologic classification offers substantial advantages to the current diagnostic studies including autoantibody determination.

In addition to these studies, the March issue of N2 contains other interesting articles that I hope will draw your attention.

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Disclosure

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