ANTI-MUSK MYASTHENIA PRECEDING B-CELL LYMPHOMA

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Case Report. A 50 years old woman developed a fluctuating speech disorder characterized by difficulties in the pronunciation of the labial consonants. Over the subsequent 6 months the dysarthria worsened and a persistent bilateral ptosis and mild dysphagia. The search for anti-acetilcholin receptor antibodies (AchRab) and an EMG gave negative results. After a sudden worsening she was admitted to our Neurology Clinic. The neurological examination confirmed a mild bilateral and diplopia associated with a fluctuating second degree nystagmus beating to right. Medical history reported a voluminous uterine fibroma. Since brain MRI showed multifocal lesions in the white matter of unclear interpretation, a lumbar puncture was performed, but standard CSF parameters were normal and no intrathecal IgG synthesis (IgGOB) was demonstrated. The clinical picture suggested the diagnosis of AchR ab-negative myasthenia gravis (MG) and thus the presence of **serum anti-MUSK antibodies** was investigated. In waiting for the answer of this test, therapy with IGIV was started with slowly but progressive improvement. Furthermore, the possible paraneoplastic origin of the syndrome was also investigated. A total body CT scans (with contrast) revealed three lesion compatible with fibroid uterine and multiple enlarged lymph nodes in periaortic, interaortocaval and mesenteric district. A total body PET-TC examination, however, was completely normal (Figure 1). Finally, the search for anti-MUSK antibodies was positive and the diagnosis of anti-MUSK MG was definitely achieved. Immunosuppressive therapy with azathioprine was started, and therapy with plasma exchange was continued for three months. The patient remained neurologically stable for one year with repeated blood cell count and differentiation values always in the normal range (occasional mild decrease in lymphocyte number (800/ul) was observed).

Then, the patient suddenly developed an acute respiratory distress. Chest RX revealed **enlarged mediastinic lymph nodes**: total body CT scans confirmed these findings (Figure 2), showing also an involvement of periaortic and mesenteric district.

PET-scan revealed a diffuse lymph node captation. Histological examination on bioptic sample revealed **a large B cell lymphoma.**

Rituximab therapy associated with CHOP was immediately started, but the patient rapidly developed a marked lymphopenia and died for pulmonary infection.

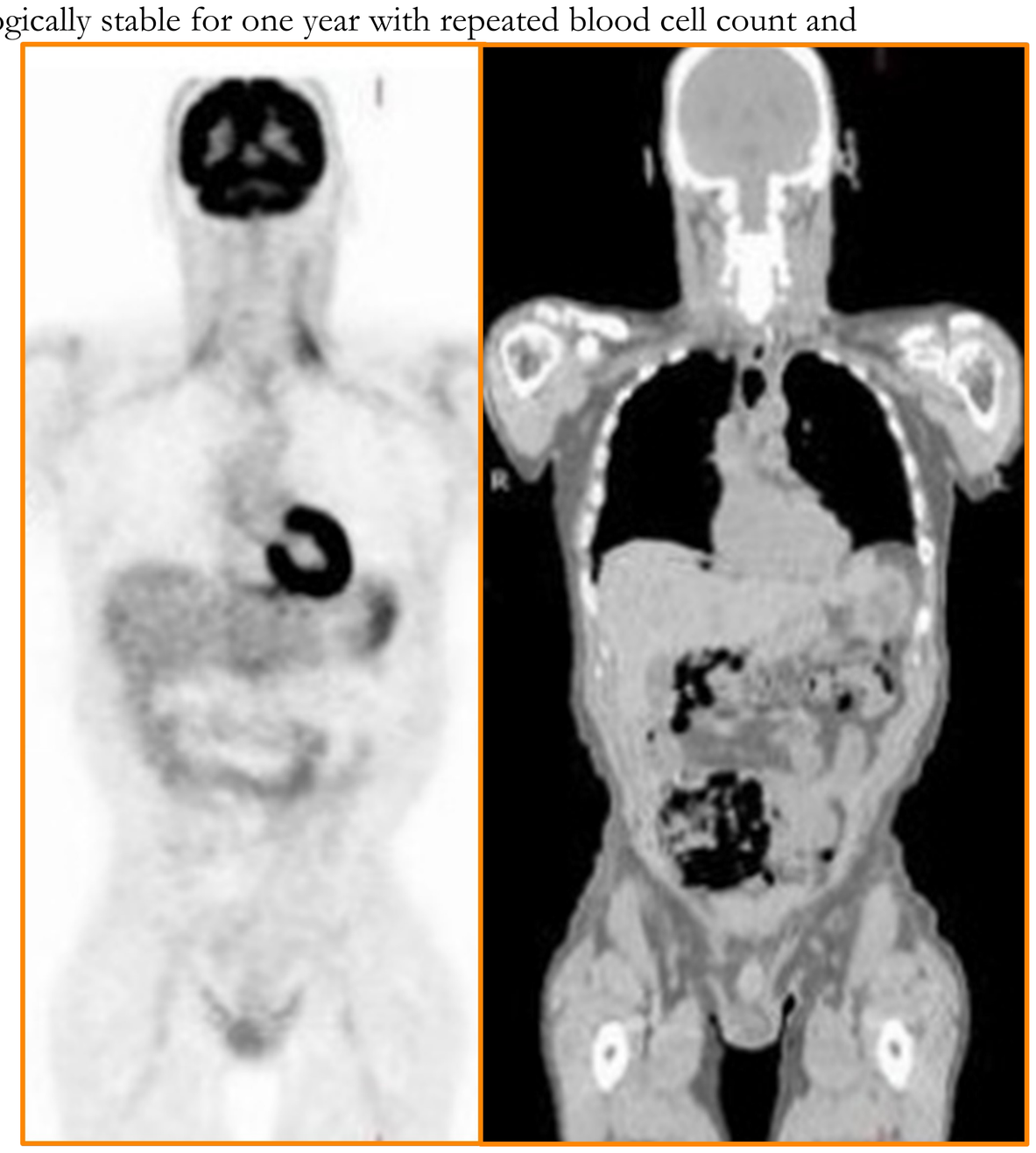

Figure 1. 18-FDG PET-CT performed at baseline did not dislcose any abnormal glucose intake.

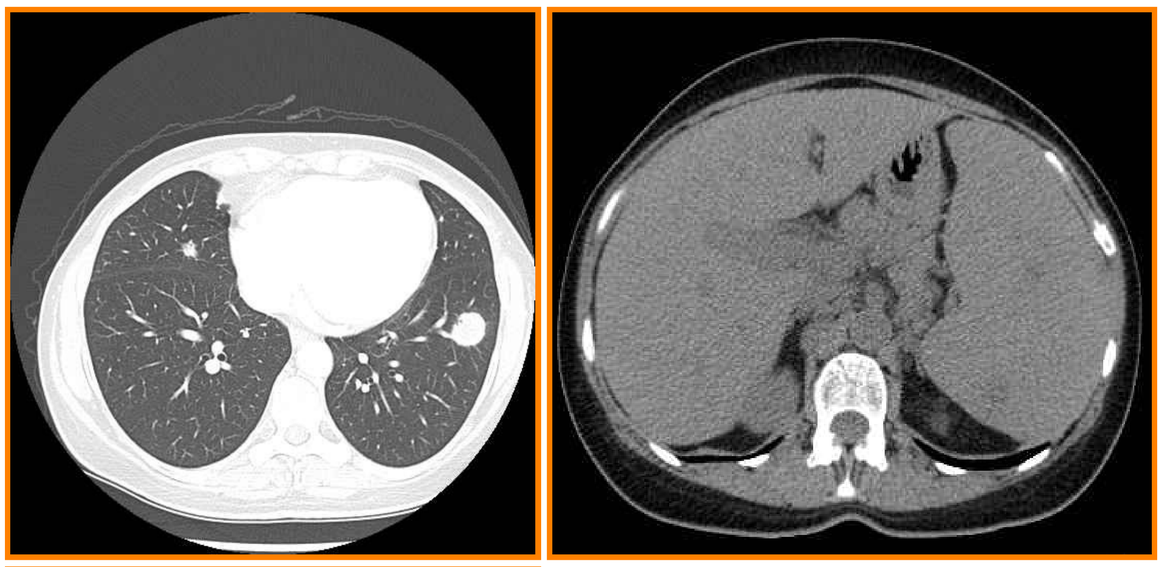

Figure 2. CT scans confirmed enlarged mediastinic lymph nodes.

Discussion.

Anti-MUSK mediated MG constitutes a clinically and serologically defined subgroups of patients. Many evidences support the hypothesis of a deregulation of follicular T-cells that enhance the survival of auto reactive B-cells (Figure 3). Moreover, serum BAFF is a molecule involved in B-cell survival, which was demonstrated to be higher in the serum of MUSK-meditated MG patients (Figure 4). All these data suggest that an autoreactive B-cell survival is enhanced by BAFF and by a deregulation of follicular response. Moreover, BAFF is also involved in lymphomagenesis, since it stimulates the proliferation of B cells effecting on multiple pathways, including mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase(PI3K), and they also converge on the activation of the NF-$\varkappa$B transcription complex.

Since an association between neoplasy and azathiprine have been demonstrated only for skin cancer (not melanoma) with higher dosage or with long-term administration, it seems unlikely that this immunosuppresive therapy could have induced limphoma in our patient.

Conclusions: This case points out the possible association of Anti-MUSK myasthenia gravis with B cell lymphoma. Indeed, the temporal sequence of the two pathologies suggests the **possible paraneoplastic nature of the autoimmune disease**, that, as in others paraneoplastic neurological disorders, could have preceded the appearance of the proliferative B-cell pathology. It might be conceivable a neoplastic-induced impaired B-cell clonal selection and proliferation.

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