Extended Abstract

Clinical and laboratory features heralding the appearance of thymoma: extended abstract

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Introduction

Thymic malignancies are tumours of the anterior mediastinum. While rare, their association with a variety of paraneoplastic disorders has led to them being extensively studied. The most common and best understood of these associations is with Myasthenia gravis (MG). MG is an autoimmune disease of the neuromuscular junction causing weakness of the skeletal muscle. While several antibodies have been identified in association with MG, only those against acetylcholine receptors (AChR) and muscle specific kinase (MuSK) are routinely used clinically, and only AChR antibodies have an association with thymic pathology. Overall, 15% of patients with MG have thymoma, while up to 50% of patients with thymoma have MG (1). While there is no definitive marker of the presence of a thymoma in MG, there are several clinical and laboratory indicators which should raise suspicion. Here, we discuss some of these indicators.

MG and thymoma

Clinical features of MG

MG associated with thymoma can present with the full spectrum of clinical features seen in MG without thymoma. However, certain characteristics are more common. While MG incidence has a bimodal distribution and the risk of thymoma overall increases with age, peaking in the seventh decade, the peak incidence of MG with thymoma is in the fourth to sixth decades of life (2,3). MG in association with thymoma is more likely to be severe, with increased frequency of early bulbar, respiratory and neck muscle involvement. Limbs can be relatively spared (4). It is also important to a new or recurrent thymoma in patients who become more symptomatic or treatment resistant without a clear cause, having been previously stable.

Laboratory features of MG

The presence of anti-titin and anti-ryanodine receptor (anti-RyR) antibodies are associated with the presence of thymoma in some MG patients. These antibodies are not pathogenic, or specific for MG. Anti-titin antibodies are present in approximately 30% of all MG patients with AChR antibodies, but this number increases to as high as 90% of patients with thymoma and MG (5-7). However, approximately 50% of patients with late onset MG (LOMG) without thymoma also have anti-titin antibodies, with the proportion of anti-titin positive patients increasing linearly from 40% in the sixth decade to 88% in the ninth decade of life (5). Overall, anti-titin antibodies have a 90% positive predictive value (PPV) and 95% negative predictive value (NPV) in early onset MG (EOMG) and 71% PPV and 55% NPV in LOMG. Therefore, the presence of anti-titin antibodies as an indicator of possible underlying thymoma can be of use in EOMG and should precipitate careful investigation for a thymoma (5). Similar to anti-titin antibodies are anti-RyR antibodies. These can be present in 50–70% of patients with AChR antibodies and thymoma and up to 20% LOMG patients without thymoma. As a result, their use is primarily in EOMG as well (1,7-10). It is notable that anti-RyR antibodies are associated with increased frequency of bulbar, neck weakness at disease onset, while anti-titin antibodies are

associated with more frequent respiratory involvement, though bulbar involvement is also more common (5,11,12). This is in keeping with the clinical findings observed in MG with thymoma. At present, anti-titin antibody testing is more available than anti-RyR and therefore is used more frequently in the clinical setting.

Metastases and other paraneoplastic syndromes

It is important for a clinician to be aware of the spectrum of symptoms thymoma can cause beyond MG. Local invasion of the lung and pleura can cause chest pain and breathlessness, while superior vena cava obstruction is well recognised. Rarely, distant metastases can spread to locations such as liver and adrenal glands and should be considered (13). Furthermore, many paraneoplastic syndromes can be seen with thymoma and up to 15% of patients with thymoma will develop a paraneoplastic syndrome other than MG. Therefore, patients with MG who display clinical features suggestive of other paraneoplastic syndromes should be aggressively investigated. These may include anaemia, hypogammaglobulinaemia, alopecia, lichen planus and many others (14,15).

Infection and thymoma

Infections are commonly seen in patients with MG. Often, these can be attributed directly to their MG, such as with aspiration pneumonia or due to immunosuppression. However, in the event of recurrent infections or opportunistic infections, one must consider other possibilities that could relate to an underlying thymoma.

Good syndrome

One well recognised cause of such infections is Good syndrome. A paraneoplastic disorder that results in hypogammaglobulinaemia, low or absent B cells in peripheral blood and, in some cases, changes in T-cell mediated immunity as well. However, one must exercise caution when interpreting such laboratory findings as rituximab can produce a similar effect. Infections commonly associated with Good syndrome usually affect the upper and lower respiratory tracts with bronchiectasis sometimes developing. However, a whole range of atypical infections can occur (16).

Cytokine antibodies

Many cytokine antibodies have been identified, some of which are associated with thymoma, immunodeficiency and infection (17). It is unclear which of these are pathogenic. Some appear to be associated specifically with thymoma patients who develop opportunistic infections while others do not (18). Interferon-α and interferon-ω antibodies are found to be elevated in thymoma regardless of infection, but interleukin (IL)-12 p35 and IL-17 are specifically elevated in patients with thymoma and opportunistic infections (7,18). Certain cytokine antibodies such as those against as IL-12, IL-22 and IL-17 are associated with particular infections such as chronic mucocutaneous candidiasis, while others can be associated with a range of mycobacterium, cryptococcal infections or severe bacterial infections. The presence of such infections should precipitate in-depth investigation for an underlying thymoma (14,17,19). It is likely that rather than a single cytokine antibody being responsible, various combinations of antibodies result in immunodeficiency predisposing to different infections.

Conclusions

In conclusion, the presence of anti-titin or anti-RyR antibodies in EOMG, or the presence of bulbar or respiratory symptoms, should raise the possibility thymoma. In addition, it is important to be aware of other associated paraneoplastic syndromes and to have a low threshold to investigate for thymoma in those with persistent or opportunistic infections.

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