DEAR EDITOR, Good syndrome is a clinical condition of immunodeficiency due to hypogammaglobulinaemia and B cell depletion in patients with a (history of) thymoma, leading to infections and autoimmune complications (1). Haematological malignancies have rarely been described in Good syndrome. We here describe a B cell deficient patient with Good syndrome complicated by two independent haematological malignancies of B cell origin. A 70-year-old male with recurrent episodes of pneumonia and oesophageal candidiasis was referred to our outpatient clinic for immunodeficiency analysis. Six years prior, he had received curative treatment for a 8x9 cm pT1N0M0 type AB thymoma by radical surgical resection (Figure 1A-B). There was no evidence of recurrence to date. He reported a history of chronic obstructive pulmonary disease (GOLD classification II), IgG-lambda monoclonal gammopathy of unknown significance (MGUS) since two years and pancreatic insufficiency (see Supplementary Table S1, available at Rheumatology online, for detailed patient characteristics).

His laboratory results indicated low levels of IgM and IgA (0.3 g/l (normal range: 0.4–2.3)) and 0.6 g/l (0.7–4.0), respectively), but high levels of IgG (20.1 g/l (7.0–16.0), of which 18.4 g/l monoclonal IgG-lambda protein) and increased free lambda light chain (60.9 mg/l (8.3–27), with a kappa/lambda ratio of 0.29 (0.31–1.56)). Previously, at the time of the thymoma treatment, immunoglobulin titers were not measured. A pneumococcal vaccination demonstrated inadequate anti-pneumococcal antibody response. Additional flow cytometry lymphocyte subset analysis repeatedly revealed a complete absence of B (CD19+) lymphocytes or plasma cells (CD38+ CD138+) (Supplementary figure S1, available at Rheumatology online). Natural killer (NK) cells, CD4+ and CD8+ T cells were identified in normal absolute amounts. There was no evidence for HIV infection.

Good syndrome was diagnosed based on the history of thymoma, absence of circulating B cells and immunodeficiency with recurrent infections. Treatment with intravenous immunoglobulins (IVIG) 0.4 gram per kilogram in combination with prophylactic azithromycin and fluconazole was initiated. High levels of monoclonal IgG in absence of circulating B cells as a feature of Good syndrome has not previously been described (2). Bone marrow biopsy showed presence of all three hematopoietic cell lines, a complete absence of B cells and a markedly increased presence of 15% plasma cells (CD38+, CD138+ cells) by volume, expressing IgG-lambda immunoglobulin (Figure 1C-D). In the absence of lytic bone lesions, anaemia, hypercalcemia or renal insufficiency, we classified the plasma cell proliferation as a smouldering myeloma (3).

Several months later, our patient reported novel complaints of redness, irritation and swelling around the left eye. A computed tomography scan revealed a subconjunctival mass. Additional conjunctival biopsy demonstrated >95% CD20− PAX5− CD79a− BCL2−, CD10− CD23− BCL6− monoclonal B cells with wt-MYD88, fitting a diagnosis of mucosa-associated lymphoid tissue (MALT) lymphoma (Figure 1E-F). CD138 staining revealed no significant plasma cell presence in this biopsy. Patient was referred for 2x2Gy palliative radiotherapy.

A literature study of Good syndrome yielded only four cases with concurrent (pre)malignant haematological neoplasms: two MGUS (4, 5), one CD8+ T-Cell large granular lymphocyte leukaemia (6) and one polycythaemia vera (7). Therefore, we believe that we here present the first case of smouldering myeloma and MALT lymphoma in a patient with Good Syndrome, and the first with multiple malignancies.

The underlying mechanism or genetic basis for Good syndrome is poorly understood (8). The limited number of reported cases precludes assessment of a causal relationship between haematological malignancies and Good syndrome. Therefore, we recommend systematic evaluation and registration of malignant diseases in thymoma patients, especially those diagnosed with Good Syndrome, especially since such cases give unique insights in malignant cell behaviour without interference from healthy B (lineage) cells.

The years-long timeline between curation of the thymoma and onset of the B cell malignancies in this patient raises questions about the malignancies’ cell(s) of origin. Two distinct explanations may be offered: either cells of B cell lineage underwent malignant transformation and then laid dormant for years preceding their clinical manifestation, or very indolent cell types residing in peripheral tissues, such as long-lived plasma cells and memory B cells, retain a malignant potential. Such a conclusion warrants re-evaluation of
the contribution of the memory compartment to malignant B cell diseases.

The development of a B cell malignancy and independent plasma cell malignancy, raises the question whether alteration of the cellular immune system after development of a thymoma and particularly after diagnosis of Good syndrome, increases the risk for hematological malignancies. It is currently unclear whether Good syndrome influences tumour suppression potential, whether the B cell depleted state induces stimulation of the remaining B lymphocytes and plasma cells or whether the co-occurrence of two different hematological malignancies and thymoma might reflect underlying dysregulation of immunity and B cell differentiation. In order for any of these questions to be answered, a systematic collection and description of cases with concurrent Good Syndrome and B cell lineage malignancies is required. Such efforts could lead to extended screening indications for Good syndrome patients and an improved understanding of this enigmatic disease.

Acknowledgements

We are grateful to Dr Els Ahsmann and Dr Rob Verdijk for providing the pathology slides displayed in this manuscript.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.
Disclosure statement: The authors have declared no conflicts of interest

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Accepted 14 September 2020
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