Hypogammaglobulinaemia in identical twin sisters with rheumatoid arthritis

Sirs,

A now 62-year-old woman (patient 1) has been under care for severe anti-citrullinated protein antibody-positive rheumatoid arthritis (RA) at our clinic since her diagnosis in 2000. She received different disease-modifying anti-rheumatic drugs (DMARDs, Fig. 1). Additionally, she required low-dose prednisone being later replaced by modified-release prednisone due to pronounced morning stiffness. In combination with etanercept, this ensures remission to date.

Shortly after the diagnosis of RA, patient 1 developed complicated shingles with postherpetic neuralgia. Afterwards, she did not show an increased susceptibility for infections for years (Fig. 1). However, in 2009 she needed outpatient treatment for shingles and pneumonia. One year later, patient 1 started suffering from frequently recurring skin infections and abscesses which needed surgical treatment repeatedly. In 2013, we firstly detected a significant hypogammaglobulinaemia (5.7–6.5g/l); IgA (1.78g/l) and IgM (2.09g/l) levels were normal. Blood cell count showed slightly increased leukocytes (10.800/µl). Further flow cytometric phenotyping of lymphocytes revealed slightly increased T cell but normal B cell counts (CD3 2275/µl, CD4 1820/µl, CD8 315/µl, CD19 350/µl). Among B cells, transitional cells (4.2/l), memory cells (33.6/µl) and plasmablasts (1.1/µl) were normal, while naïve and plasma cells were slightly increased (263.9 and 4.6/µl, respectively). Due to recurring infections including an oral candidiasis, supplementation of intravenous immunoglobulin (IVIG) was initiated and is applicated regularly until today. Keeping the IgG serum levels above 7g/l led to a marked improvement with fewer infections.

The identical twin sister, patient 2, was diagnosed with RA in 2014. Contrary to her sister, the RA took a markedly mild course. Therapies included methotrexate (MTX), leflunomide and certolizumab-pegol. After the initial treatment, glucocorticoids were tapered off rapidly. She has been receiving certolizumab-pegol/MTX for 4 years now and is in enduring remission. A significant hypogammaglobulinaemia (5.48g/l) was revealed in 2017. Interestingly, to date, patient 2 never developed any relevant infection, thus supplementation of IVIG was never necessary. Neither of the sisters had any extraarticular manifestations.

Due to the patient's close relationship and the coincidental RA, we considered whether or not the detected hypogammaglobulinaemia was a secondary entity (1). With unchanged levels of IgA/IgM as well as normal B and increased T cell counts in patient 1, a common variable immunodeficiency disorder (CVID) as a primary cause could be excluded according to the 2018 classification criteria of the European Society for Immunodeficiencies (ESID) (2). Investigating possible secondary reasons, a loss due to renal/digestive leakage (1) could be ruled out. Furthermore, neither complete blood count nor additional laboratory testing (unsuspicious serum albumin and protein electrophoresis, no proteinuria) found any evidence for a haematological disorder. In both patients, therapy was initiated using MTX. Either of them required treatment changes and both were prescribed leflunomide at some point. While hypogammaglobulinaemia under rituximab therapy is especially well-known (3), also DMARDs (4-9) and glucocorticoids in particular can be causative (9). Since patient 2 only got glucocorticoids for a short period and patient 1 showed normal B cell counts without the specific cytofluorimetric pattern described in (9), we excluded glucocorticoids as the primary cause. We also ruled out TNF inhibitors, since they are not associated with hypogammaglobulinaemia (6, 8). The only mutual DMARDs were leflunomide and MTX, so we hypothesized that the hypogammaglobulinaemia was induced by either one of them. Leflunomide, however, was only given for a short time: 3 and 4 months, respectively. This makes it an unlikely cause, even though a small study found the incidence of hypogammaglobulinaemia under leflunomide to be increased almost 8-fold, while MTX only showed a 2-fold increase (6). MTX was used for 10 years in patient 1 and is still part of the ongoing therapy in patient *2*. It has been found to significantly reduce IgM in particular (8). While not reducing memory cells (10), MTX has a negative impact on transitional cells (8).

Summing up those findings, the DMARDs used are not likely the reason for the observed hypogammaglobulinaemia. Because of the patient's close relationship, there are most likely unrevealed genetic causes with qualitative impact on the B cell pool involved. Why patient 2 never developed any infectious complications at all remains elusive. One possible explanation might be the continuous need of glucocorticoids in patient 1, which could have contributed to the susceptibility for infections.

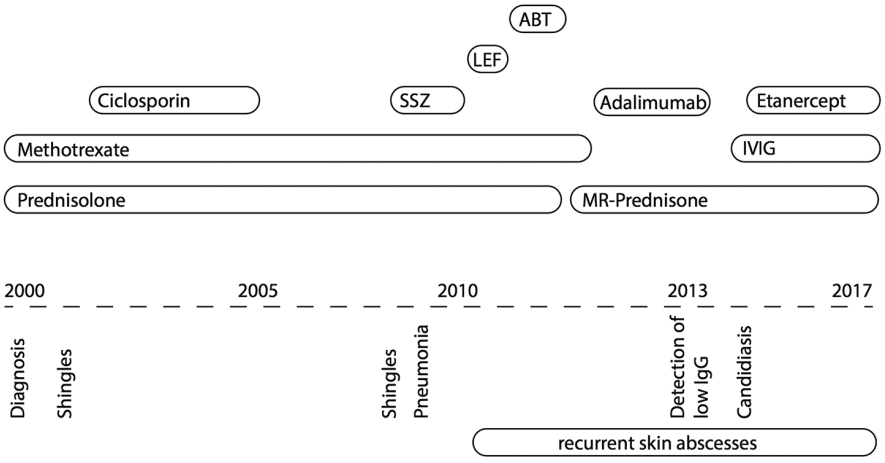

Fig. 1. Therapy course and infectious complications of patient 1 during outpatient care.
ABT: abatacept; IVIG: intravenous immunoglobulin; LEF: leflunomide; MR-Prednisone: modified-release prednisone (Lodotra®); SSZ: sulfasalazine.

Ethical approval

All procedures performed in this survey were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Data obtained in this study did not interfere with the course of treatment for patients included.

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References

1. SAMSON M, AUDIA S, LAKOMY D, BONNOTTE B, TAVERNIER C, ORNETTI P: Diagnostic strategy for patients with hypogammaglobulinemia in rheumatology. *Joint Bone Spine* 2011; 78: 241-5.
2. ESID Registry - Working Definitions for Clinical Diagnosis of PID 2018 [updated 21-Jun-2018. Available from: https://esid.org/content/download/16647/453306/file/ESIDRegistry_ClinicalCriteria.pdf.

3. ROBERTS DM, JONES RB, SMITH RM *et al*.: Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. *J Autoimmun* 2015; 57: 60-5.
4. BIASI D, CARLETTO A, CARAMASCHI P, PACOR ML, MALEKNIA T, BAMBARA LM: Efficacy of methotrexate in the treatment of ankylosing spondylitis: a three-year open study. *Clin Rheumatol* 2000; 19: 114-7.
5. LEE AH, LEVINSON AI, SCHUMACHER HR JR: Hypogammaglobulinemia and rheumatic disease. Semin Arthritis Rheum 1993;22:252-64.
6. NEUMANN C, PROFT F, HAMMITZSCH A, GRUENKE M, SCHULZE-KOOPS H: Hypogammaglobulinemia is a frequent finding in patients under immunosuppressive therapy but does not correlate with susceptibility to infections. *Ann Rheum Dis* 2013; 72: A338.
7. WIESIK-SZEWCZYK E, KUCHARCZYK A, SWIERKOCKA K, RUTKOWSKA E, JAHNZ-ROZYK K: Recurrent infections in a patient with psoriatic arthritis and hypogammaglobulinemia, treated with conventional and biologic disease-modifying antirheumatic drugs-a primary or secondary entity? *Clin Rheumatol* 2017; 36: 1677-81.
8. GLAESENER S, QUACH TD, ONKEN N *et al*.: Distinct effects of methotrexate and etanercept on the B cell compartment in patients with juvenile idiopathic arthritis. *Arthritis Rheumatol* 2014; 66: 2590-600.
9. WIRSUM C, GLASER C, GUTENBERGER S *et al*.: Secondary antibody deficiency in glucocorticoid therapy clearly differs from primary antibody deficiency. *J Clin Immunol* 2016; 36: 406-12.
10. ANOLIK JH, RAVIKUMAR R, BARNARD J *et al*.: Cutting edge: anti-tumor necrosis factor therapy in rheumatoid arthritis inhibits memory B lymphocytes via effects on lymphoid germinal centers and follicular dendritic cell networks. *J Immunol* 2008; 180: 688-92.