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 post-herpetic 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 (1.79g/l) and IgM (2.09g/l) levels were normal. Blood cell count showed slightly increased leucocytes (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 (4.2/1), 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 applied 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 immunodefi- ciency 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 lefluno mide 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 cytotoxic fluorometric 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.

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


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