Management of hypogammaglobulinaemia occurring in patients with systemic lupus erythematosus

P. F. K. Yong1,2, L. Aslam2, M. Y. Karim2,3 and M. A. Khamashta2

Objectives. Systemic lupus erythematosus (SLE) is typically associated with hypergammaglobulinaemia but has been described in the setting of hypogammaglobulinaemia as well. The purpose of this article is to describe various cases of SLE and hypogammaglobulinaemia, review the literature and present management strategies for hypogammaglobulinaemia in SLE.

Methods. We describe five patients with SLE and antibody deficiency, and review the literature exploring the relationship between the two.

Results. Various types of antibody deficiency syndromes, including common variable immunodeficiency (CVID), IgA deficiency, IgM deficiency, drug-induced hypogammaglobulinaemia and hypogammaglobulinaemia secondary to nephrotic syndrome can occur in SLE. Antibody deficiency states can be treated with antibiotics and replacement immunoglobulin therapy (particularly CVID) but sometimes close monitoring is all that is required.

Conclusion. Measurement of immunoglobulin levels is useful in SLE to identify coexisting antibody deficiency and the later development of hypogammaglobulinaemia. This allows monitoring and appropriate treatment to be instituted.

Key words: Systemic lupus erythematosus, Primary antibody deficiency, Immunodeficiency, Hypogammaglobulinaemia, Immunoglobulin G.

Introduction

SLE is a chronic autoimmune disorder characterized by the production of a plethora of autoantibodies, many of which are directed against nuclear antigens. Characteristic autoantibodies include anti-dsDNA and anti-Sm antibodies. Polyclonal hypergammaglobulinaemia is a well-recognized laboratory abnormality in SLE. However, various forms of hypogammaglobulinaemia, both congenital and acquired, can occur in patients with SLE. These include selective IgA deficiency [1, 2], common variable immunodeficiency (CVID) [3, 4], drug-induced hypogammaglobulinaemia [5] and hypogammaglobulinaemia secondary to nephrotic syndrome.

Treatment of SLE involves the administration of a variety of immunosuppressive and immunomodulatory drugs. Side-effects include complications from infection and in some cases, this is related to immunodeficiency such as hypogammaglobulinaemia. In some cases, a specific drug can be identified as the trigger for the development of hypogammaglobulinaemia, whilst in other settings this may not be so clear.

The management of hypogammaglobulinaemia occurring in the context of SLE is important to consider. Although there are effective treatments, including intravenous immunoglobulin (IVIg) replacement, not all patients will require intervention. In some cases, watchful waiting may be more appropriate than immediate treatment. In this report, we discuss various cases of hypogammaglobulinaemia complicating SLE, and discuss their management and prognosis.

Methods

Literature review

A review of published literature was undertaken using a search of the PubMed database available from the National Library of Medicine. Key articles on SLE and hypogammaglobulinaemia were identified and further articles of interest were identified by hand searching the relevant literature.

Case reports

Case 1: selective IgA deficiency

A 23-yr-old Caucasian female was initially diagnosed with SLE in 1999 at the age of 17 yrs, having previously had immune thrombocytopenic purpura. She presented with photosensitivity rash, arthralgias, livedo reticularis and autoimmune thrombocytopenia. Subsequently, she developed nephrotic syndrome in September 2001 and was admitted locally for assessment. She received treatment with cyclophosphamide and methylprednisolone that month. During admission she developed grand mal seizures in October 2001, and her brain MRI was suggestive of cerebral lupus. She was treated with high dose IVIg (400 mg/kg daily for 5 days), following which she made good recovery. She also underwent a renal biopsy that showed diffuse proliferative (WHO class IV) glomerulonephritis. Following her second cyclophosphamide infusion, she developed haemorrhagic cystitis. Cyclophosphamide was discontinued after she had received a cumulative dose of 1 g, and she was commenced on mycophenolate mofetil initially at 1g daily, which was subsequently increased to 2 g daily. She made tremendous progress following the acute episode in 2001 and progressed very well on mycophenolate mofetil, with no further acute lupus flares and good renal function.

In 2002, her immunoglobulins showed low levels of IgA and IgM, with IgG at the lower end of the normal range (Table 1). Urinalysis showed no significant proteinuria and serum albumin levels (Table 1) were normal excluding renal loss of immunoglobulins. Her very low IgA levels were compatible with a diagnosis of selective IgA deficiency. Over time, her IgM and IgG have increased, but her IgA has remained low, consistent with this diagnosis. Despite these immunoglobulin abnormalities, her clinical course has not been complicated by recurrent infection.

Case 2: drug-induced hypogammaglobulinaemia

A 37-yr-old Caucasian lady with predominantly cutaneous and renal SLE (Class IV lupus nephritis diagnosed in August 1997) had previously received intravenous cyclophosphamide therapy (total cumulative dose of 2.5 g) and methylprednisolone, followed by AZA at 150 mg daily for maintenance therapy. She was found to have low immunoglobulins, particularly of the IgG isotype in March 2003. A 24 h urine protein collection showed 1.4 g/24 h. She however gave no history of recurrent infection. Consequently, no intervention with IVIg was arranged, and the patient was carefully monitored for recurrent infection, and her immunoglobulin levels...
measured sequentially. Over time, her immunoglobulin levels increased, with the values returning to the normal range (Table 2). Her 24-h urine protein collection in July 2006 was 0.86 g/24 h. It was considered that the most likely diagnosis was a drug-induced hypogammaglobulinaemia, in view of the spontaneous improvement in immunoglobulin levels. Cyclophosphamide was thought to be the most likely candidate resulting in her temporary hypogammaglobulinaemia.

Case 3: possible CVID
A 68-yr-old Caucasian lady had a long history of SLE, dating back over 30 yrs, with previous history of lupus nephritis. Her treatment had consisted primarily of prednisolone, at a dose between 10 and 20 mg daily, although she had AZA transiently, which was discontinued due to diarrhoea, vomiting and jaundice. She had not ever been treated with cyclophosphamide. More recently, her SLE had become relatively inactive, but immunological testing revealed persistent evidence of panhypogammaglobulinaemia (IgG 1.7 g/l, IgA < 0.06 g/l, IgM < 0.05 g/l). There was no evidence of myeloma, lymphoma or thymoma; which were important to exclude as secondary causes of hypogammaglobulinaemia would be more common in a patient of this age. There was no family history of CVID or other immunodeficiency.

Her lymphocyte subsets showed reduction in B cells and CD4+ T cells. CVID was considered as a possible diagnosis. She had never been on immunosuppression more potent than oral prednisolone for any significant length of time, though drug-related hypogammaglobulinaemia is of course impossible to completely rule out. In addition, although the diagnosis is less likely in someone of her age, CVID has been reported to occur at advanced age [4] and several other causes of secondary hypogammaglobulinaemia had been sought and excluded. During her clinical course, she developed an *Escherichia coli* abscess of the thyroid, and was experiencing recurrent respiratory tract infections. Hence, she was commenced on replacement IVIg (Vigam, BPL, Herts, UK) but developed back pain a day after the first and second infusions. A different IVIg product (Octagam, Octapharma, Lachen, Switzerland) was then tried with similar side-effects and consequently the treatment was temporarily discontinued. She then died from an unrelated cause.

Case 4: hypogammaglobulinaemia secondary to nephrotic syndrome
A 21-yr-old Asian accountancy student was diagnosed with SLE at the age of 19 yrs, with features including autoimmune haemolytic anaemia, and WHO Classes III and V lupus nephritis with nephrotic syndrome. He had received intravenous cyclophosphamide (cumulative dose of 1.8 g) in July 2004 but was lost to follow-up and reattended in January 2005 with recurrence of disease. He received further intravenous cyclophosphamide (cumulative dose of 3 g) then as induction treatment, followed by maintenance therapy with AZA. However, he developed transaminitis whilst on AZA after a few days. This was discontinued and he was commenced on mycophenolate mofetil in May 2005, at a dose which was gradually increased to 2 g daily. He was subsequently found to be hypogammaglobulinaemic with a very low IgG level. His baseline and subsequent immunoglobulin levels and contemporaneous urinary protein excretion are shown in Table 3. The hypogammaglobulinaemia was considered to be a consequence of his nephrotic syndrome. Although nephrotic syndrome is a frequent complication of lupus nephritis, hypogammaglobulinaemia is uncommon. It is interesting to note that as his nephrotic syndrome improved and protein excretion reduced on mycophenolate mofetil, his IgG levels also started to improve, supporting our proposal for its aetiology. He is currently doing very well on therapy with mycophenolate mofetil, ramipril and atorvastatin, with good improvement in his proteinuria, IgG level and cholesterol.

Case 5: selective IgM deficiency
A female patient presented in her 20s with low platelets, and underwent a splenectomy the next year. Three years after initial presentation, she was diagnosed with SLE after developing facial skin lesions. Her condition involved mainly skin and joints initially, and after 20 yrs she developed a systemic flare including renal involvement, with proteinuria 7.93 g in 24 h. Renal biopsy in 1998 showed mainly membranous lupus nephropathy with some proliferative change (WHO Class Vc). She received six pulses of intravenous cyclophosphamide (cumulative dose of 3 g) at that time, followed by mycophenolate mofetil. This was continued for 6 yrs, and subsequently successfully stopped. Routine bloods in July 2006 showed IgM < 0.25, IgG 8.2, IgA 4.5 g/l. At this point, her serum albumin was normal (50 g/l) and she had no significant proteinuria on urinalysis. She reports no history of recurrent infection of her chest, sinuses or urine and her average antibiotic use is only 0–1 courses per year.

Case 6: symptoms suggestive of immunoglobulin deficiency, but with normal immunoglobulin levels
A 33-yr-old lady of Irish origin was diagnosed with SLE in 1994 with onset of symptoms in the early 1990s. Her immunology showed anti-dsDNA, anti-Ro and La antibodies and more recently anti-cardiolipin antibodies. She was commenced on AZA 100 mg daily but then developed WHO Class IV lupus nephritis in August 1999. Treatment for this over subsequent years has included prednisolone, pulsed intravenous cyclophosphamide and mycophenolate mofetil. Her disease course has been complicated by two pneumococcal infections in September 1999, prior to commencing cyclophosphamide and in January 2002; both of which required admission to the intensive therapy unit. She has subsequently developed obliterator bronchiolitis with severe respiratory impairment.
Selective IgM deficiency

Twelve of 54 Japanese patients with SLE were found to have selective IgM deficiency (defined as serum IgM < 2 S.D. below the mean). No difference in clinical features.

Selective IgA deficiency

Five out of 96 patients with SLE in an outpatient population were persistently IgA deficient. These patients were more likely to be West Indian or have anti-Sm and anti-La antibodies, but no difference in clinical features.

Selective IgG deficiency

Seventy seven children with SLE followed prospectively for ≥ 20 yrs and 152 adults with SLE surveyed during a 1-yr period. IgA deficiency identified in 2.6% of adults and 5.2% of children. No difference in clinical course or presentation.

Selective IgM deficiency

Twelve of 54 Japanese patients with SLE were found to have selective IgM deficiency (defined as serum IgM < 2 S.D. below the mean). All 12 patients were on prednisolone. Longer disease duration was associated with lower IgM levels. Median IgM levels were lower in SLE patients compared with controls.

Selective IgG deficiency

Twenty of 108 Malaysian patients and five of 22 Caucasian patients with SLE had IgM levels below the lower limit of control subjects. Median IgM levels were lower in SLE patients compared with controls.

Clinical implications

The clinical implications of hypogammaglobulinaemia are diverse. Some patients may be asymptomatic, even with very low immunoglobulin measurements. In our series, Case 4 had an IgG level of 1.7 g/l with no increase in infection. However, other patients may develop recurrent infections, such as Case 3. Infections due to hypogammaglobulinaemia are typically with encapsulated bacteria (including pneumococcus and haemophilus species) and can affect upper and lower respiratory tracts. Recurrent infections may result in the development of bronchiectasis. Table 4 summarizes the various antibody deficiency syndromes associated with SLE.

CVID and SLE

Hypogammaglobulinaemia in patients with SLE may occur as part of CVID. This is a heterogeneous group of primary immunodeficiency disorders, where the hallmark is failure of antibody production [8]. Several single gene defects have been identified resulting in a CVID phenotype but in the majority of patients the underlying cause is unknown. Patients with CVID generally develop recurrent respiratory and sinus infections. However, a subset of these patients can also develop features suggestive of immune dysregulation including autoimmunity (usually cytopenias which can be a presenting feature, but also SLE), granulomatous inflammation which can affect liver, spleen and lungs, and various forms of bowel disease. Of course, cytopenia, which is a feature of CVID, may also be explained by SLE.

CVID has been described in patients after the diagnosis of SLE [3, 4], but in virtually all published case reports, immunosuppressive agents had been used for treatment of SLE prior to detection of hypogammaglobulinaemia [3]. This clearly makes it difficult to make a definitive diagnosis of CVID or drug-related hypogammaglobulinaemia, especially as a diagnosis of CVID depends on exclusion of all other known causes of hypogammaglobulinaemia [8]. The presence of other features of CVID, such as granulomatous disease, and bowel disease can help in the diagnosis. In Case 3, though immunoglobulin levels were very low, there were none of these other features that would help towards a definitive diagnosis of CVID.

Drug-induced hypogammaglobulinaemia

A variety of immunosuppressive drugs used in the treatment of SLE have been implicated in causing hypogammaglobulinaemia. These include high dose cyclophosphamide [5], AZA [9], mycophenolate mofetil [10] and even long-term low-dose corticosteroids [11]. The effect of low dose cyclophosphamide therapy on immunoglobulin levels is not well characterized. More recently, specific B-cell-directed therapy in the form of rituximab has been increasingly used in SLE and further products are in the pipeline [12]. Repeated courses of rituximab have been associated with

Table 4. Antibody deficiency syndromes reported in association with SLE

<table>
<thead>
<tr>
<th>Antibody deficiency syndrome</th>
<th>Description</th>
<th>Reference</th>
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<tr>
<td>CVID</td>
<td>Two cases of SLE and CVID reported and 16 detailed cases of SLE and CVID identified in the literature. All patients had received prednisolone and 72% had received other immunosuppressants prior to CVID diagnosis. Sinopulmonary infections were the most frequent symptom and 89% of patients received immunoglobulin replacement therapy.</td>
<td>Fernandez-Castro et al. [3]</td>
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<td>Selective IgA deficiency</td>
<td>Clinical feature of 248 patients with CVID described of which two also had a diagnosis of SLE. Five out of 96 patients with SLE in an outpatient population were persistently IgA deficient. These patients were more likely to be West Indian or have anti-Sm and anti-La antibodies, but no difference in clinical features.</td>
<td>Cunningham-Rundles et al. [4]</td>
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<td>Selective IgG deficiency</td>
<td>Seventy seven children with SLE followed prospectively for ≥20 yrs and 152 adults with SLE surveyed during a 1-yr period. IgA deficiency identified in 2.6% of adults and 5.2% of children. No difference in clinical course or presentation.</td>
<td>Rankin et al. [1]</td>
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<td>Selective IgM deficiency</td>
<td>Twelve of 54 Japanese patients with SLE were found to have selective IgM deficiency (defined as serum IgM &lt; 2 S.D. below the mean). All 12 patients were on prednisolone. Longer disease duration was associated with lower IgM levels. Median IgM levels were lower in SLE patients compared with controls.</td>
<td>Saiki et al. [22]</td>
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<tr>
<td>Selective IgD deficiency</td>
<td>Twenty of 108 Malaysian patients and five of 22 Caucasian patients with SLE had IgM levels below the lower limit of control subjects. Median IgM levels were lower in SLE patients compared with controls.</td>
<td>Senaldi et al. [23]</td>
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Investigations were undertaken in view of her predisposition to pneumococcal sepsis. These showed normal immunoglobulin levels as well as adequate levels of specific anti-microbial antibodies (including pneumococcus, haemophilus influenzae B and tetanus). IgG subclasses were not tested because it was considered more informative to measure specific anti-microbial antibodies as providing a more dynamic readout of the immunoglobulin response [6]. Complement testing showed a consumptive pattern. Ultrasound scan of the abdomen confirmed the presence of a spleen. Lymphocyte subsets showed generalized lymphopenia related to SLE. She was commenced on prophylactic clarithromycin and has made good progress with no subsequent major infections.

Had the patient not responded to antibiotic prophylaxis, further investigations would have included testing of pneumococcal serotype-specific antibody levels pre- and, if necessary, post-vaccination with Pneumovax and/or the conjugated pneumococcal vaccine (Prevenar). Other potential treatment options would have included alternative prophylactic antibiotics and replacement dose IVIg.
hypogammaglobulinaemia [12] and it is likely that this will become a greater issue in the future as the B-cell-directed therapies gain more widespread use. Some other anti-rheumatic drugs, such as SSZ [13] have also been associated with antibody deficiency. Drug-induced hypogammaglobulinaemia is potentially reversible with cessation of therapy, unlike CVID, although the duration of post-cessation hypogammaglobulinaemia can be very prolonged.

Severe nephrotic syndrome with lupus nephritis

Lupus nephritis is a common complication of SLE (with a prevalence of 10% in Caucasian SLE patients rising to 58% in Afro-Caribbean patients and 74% in Chinese patients [14]), and is more severe in Afro-Caribbean patients [15]. It can present in a variety of ways, including renal impairment and nephrotic syndrome, and is characterized by a variety of pathology, previously classified by the WHO and more recently by the International Society of Nephrology and the Renal Pathology Society [16]. Nephrotic syndrome is a common presentation of lupus nephritis, and can result from various different pathologies, typically membranous (Class V), proliferative (Classes III, IV) or mixed classes of lupus nephritis. Levels of proteinuria can be high and can sometimes result in significant IgG loss as seen in Case 4. IgA and IgM levels tend to be better preserved as these are larger molecules and tend not to be lost unless there is severe protein leak in nephrotic syndrome. Although an increase in the rate of severe infections in children with nephrotic syndrome has been noted [17], there is little data correlating this with total immunoglobulin levels. There is also no data examining the prevalence of severe infections in patients with nephrotic syndrome secondary to lupus nephritis.

Selective IgA deficiency

Selective IgA deficiency is the commonest primary immunodeficiency disorder, with a prevalence of between 1 in 300 and 1 in 700 [18]. It is usually asymptomatic, with most patients requiring no treatment. However, despite this a very large number of specific disorders have been reported in association with IgA deficiency. These include recurrent sinopulmonary infections, allergy, autoimmunity, gastrointestinal diseases, malignancy, endocrinopathy and neurological diseases [19]. The spectrum of autoimmune disease reported includes RA, morphea, cryoglobulinaemia, Type 1 diabetes, autoimmune liver and thyroid disease, autoimmune cytopenias and the anti-phospholipid syndrome as well as asymptomatic autoantibody formation [19–21]. Patients who have other associated immune defects, such as an IgG2 subclass deficiency are more likely to be symptomatic with recurrent infections [19]. Rankin et al. [1] specifically investigated the occurrence of IgA deficiency in SLE and reported a prevalence of 5% in 96 SLE patients in their cohort, suggesting a significant association. More recently, Cassidy et al. [2] estimated the prevalence of IgA deficiency at 2.6% in adults (n = 152) and 5.2% in children (n = 77) with SLE. These particular patients did not have an altered clinical course compared with SLE patients without IgA deficiency. The association between IgA deficiency and autoimmunity/SLE is not completely understood although various hypotheses have been suggested, as discussed subsequently.

Selective IgM deficiency

Selective IgM deficiency is a poorly characterized immunodeficiency disorder, generally regarded as uncommon and absent from the recently published practice parameter on primary immunodeficiency [18]. We consider that IgM deficiency does not usually result in recurrent infection. Selective IgM deficiency has been described in patients with SLE and there is a suggestion that it correlates with more severe or long-standing SLE [22–25]. Some patients with selective IgM deficiency have been noted to have recurrent sinopulmonary infections, in a recently published case series [26], and these have generally responded to conventional courses of antibiotics without the need for prolonged antibiotics or IVIG therapy.

Other causes of hypogammaglobulinaemia

Other unrelated causes of hypogammaglobulinaemia can also occur in patients with SLE. Lymphoproliferative disorders, including myeloma, chronic lymphocytic leukemia and lymphoma can result in reduction in immunoglobulin levels. Lymphoma of course is associated with both SLE and pSS. Consequently, it is important to perform a serum and urine electrophoresis and other investigations as appropriate to exclude lymphoproliferative disease. This is particularly relevant in more elderly patients, as hypogammaglobulinaemia is more likely to be due to neoplastic disease than a primary antibody disorder.

Relationship between SLE and antibody deficiency

Patients with primary antibody deficiency have an increased incidence of autoimmune disease, including SLE. It has been postulated that persistent antigen stimulation, recurrent tissue damage, defective clearance of immune complexes and immune dysregulation seen in various primary immunodeficiency states all contribute towards the development of autoimmunity [27]. The mechanisms resulting in B-cell dysfunction and antibody deficiency in SLE are not known, although there has previously been speculation that development of B-cell-specific autoantibodies, early senescence of hyperactive B cells or B-cell maturation defects might be responsible [28]. Defects in regulatory T cells have been described both in SLE [29] and CVID [30] and it is possible that a common, and as yet unidentified regulatory defect might result in both these diseases.

More recently, mutations have been identified in transmembrane activator and calcium-modulator and cyclophilin ligand (CAML) interactor (TACI), a molecule involved in signalling to B cells, which might potentially shed some light on a common genetic link between primary antibody deficiency and SLE. Defects in TACI are thought to account for ~10% of patients with CVID or selective IgA deficiency [31, 32]. In addition, elimination of TACI in mice has been shown to cause lupus-like features, including B-cell hyperplasia, autoantibody formation and glomerulonephritis [33]. The co-occurrence of SLE and CVID as well as the increased prevalence of SLE in IgA deficiency suggested that this would be fertile ground for further investigation. Nonetheless, a single study failed to show any association between TACI mutations and human SLE [34] although further work is ongoing.

It has also become clear that several patients who previously were diagnosed as having CVID have been re-classified with the availability of new genetic tests. Thus, some patients previously considered to have CVID have now been shown to have X-linked gammaglobulinemia [35] or X-linked lymphoproliferative syndrome [36]. Other genetic defects described in CVID include defects in ICOS (inducible co-stimulator), CD19, BAFF-R (B-cell activating factor receptor) and Msh5 [37, 38]. However, no association with SLE has been described with any of these newly described genetic defects.

Other aspects of SLE and immune system function

Case 6 highlights the fact that similar presentations of recurrent infection with encapsulated bacteria such as pneumococcus may also occur with deficiencies of other components of the immune system apart from immunoglobulins, such as the complement proteins, spleen and neutrophils.

Complement and mannose-binding lectin. The complement system is a group of plasma and cell-surface proteins with...
important roles in innate immunity. It is responsible for mediating damage in SLE, but paradoxically deficiencies in the early components of the classical pathway (C1q, C2 and C4) predispose towards the development of lupus. It is speculated that genetic deficiencies in these components contribute towards pathogenesis of lupus by decreasing capacity for immune complex handling, aberrant tolerance induction and/or their influences on cytokine production. Genetic deficiencies in C3, the component common to all three complement-activation pathways, result both in recurrent infections and immune complex manifestations. Terminal component (C5–C9) deficiencies predispose towards recurrent neisserial infection but not SLE. An in-depth discussion of the role of complement deficiency in lupus is reviewed in ref. [39].

The role of mannose-binding lectin (MBL) in SLE is less clear; there is data to suggest that MBL deficiency might be associated with SLE although this finding is not universal. In addition, some investigators have found an increased frequency of pulmonary infection in SLE patients with MBL deficiency [40] although this has not been replicated by others [41]. Consequently, the contribution of MBL deficiency in SLE remains to be fully elucidated.

Allergy. An increased rate of drug allergy in SLE has been noted in the literature [42]. However, this finding has not been universal and a more recent study only found an increase in cutaneous reactions to sulfa antibiotics [43]. Reasons suggested for the discrepancy have included different groups used as controls. Studies looking more generally at allergy and atopy in SLE have also generated conflicting results [44–46]. In general, the studies on allergy in SLE have been small and few in number; and it is likely that this is part of the reason for differing results. Further work remains to be done to conclusively establish if SLE patients are more prone to allergic disease.

Treatment decisions in hypogammaglobulinaemia

In patients found to have hypogammaglobulinaemia, treatment decisions depend both on clinical and laboratory parameters. The principal clinical parameter that needs to be taken into account is the presence of recurrent infection. Ideally, microbiological confirmation of this should be sought. The severity of infection should be assessed and surrogate measures for this include the amount of antibiotic use, the number of infections per year (and whether there is seasonal variation) and days off work in hospital due to sickness. In addition, evidence of end-organ damage due to infection (e.g. lung function, CT chest for bronchiectasis—in CVID specifically, we avoid frequent repetition because of radiosensitivity and increased lymphoma risk) should also be sought as this sways the treatment decision towards more aggressive therapy.

Laboratory parameters that should be weighed in the treatment decision include the ability to generate specific antibodies against T-dependent and T-independent microbial antigens pre- and post-vaccination. This represents the most useful in vivo investigation assessing a subject’s immune response from antigen processing and presentation up to activation of antigen-specific B cells to mount an appropriate immune response. The absolute immunoglobulin level can also play a role in treatment decisions, especially if they are extremely low and if there is recurrent infection.

Options for treatment of hypogammaglobulinaemia

Asymptomatic hypogammaglobulinaemia does not usually warrant any intervention apart from watchful waiting, as in Cases 2, 4 and 5. Other components of the immune system can compensate for the hypogammaglobulinaemia, with no increase in the level of infections. It may also be that the ability to produce specific antibodies in response to infection or vaccination is maintained, despite the overall hypogammaglobulinaemia. Careful monitoring of the patient’s clinical status especially with regard to the frequency of infections, appropriate vaccinations (with monitoring of post-vaccination antibody levels where available) and periodic measurement of immunoglobulin levels might be all that is necessary in these cases.

Should there be an unacceptable frequency of infections or evidence of end-organ damage secondary to infection, then further specific therapy needs to be considered. Any infections that develop should be treated promptly with bactericidal antibiotics, usually a prolonged course of at least 10 days. In addition, continuous antibiotic prophylaxis might be necessary. If there is significant seasonal variation in infection rates, then different therapies can be used in winter and summer months. Finally, immunoglobulin replacement therapy, which can be given intravenously or subcutaneously in hospital or at home, should be considered depending on infection severity, underlying immunological diagnosis, evidence of end-organ damage and patient preference. Immunoglobulin preparations contain predominantly the IgG immunoglobulin isotype and only traces of the other isotypes. Consequently, replacement immunoglobulin is only indicated when the deficiency is in some form of IgG production. In addition, although relatively safe, it should be noted that immunoglobulin is a pooled blood-derived product from several thousand donors and carries the risks attendant with this.

Conclusion

Various immunoglobulin deficiency states can co-exist with SLE. These can be a result of a common aetiology or be secondary to the SLE or its treatment. Consequently, routine measurement of immunoglobulin levels in patients with SLE is valuable in helping to identify those patients at greater risk of susceptibility to infection. Effective therapies exist for treatment of hypogammaglobulinaemia and these can be utilized to improve the care of such patients, once they have been identified. Finally, further work needs to be done to increase insight into the common links that can result in both the autoimmunity seen in SLE and various immunoglobulin deficiency states, in order to better understand the immunopathogenesis and develop better therapies for the future.

Rheumatology key messages

- Antibody deficiency may occur in the context of SLE.
- Immunoglobulin levels should be checked to enable identification of deficiency monitoring and appropriate treatment.

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