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IgM monoclonal gammopathies of clinical significance: diagnosis and management

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Abstract

IgM monoclonal gammopathy of undetermined significance is a pre-malignant condition for Waldenstrom Macroglobulinaemia (WM) and other B-cell malignancies, defined by asymptomatic circulating IgM monoclonal protein below 30 g/l with a lymphoplasmacytic bone marrow infiltration of less than 10%. A significant proportion, however develop unique immunological and biochemical manifestations related to the monoclonal protein itself in the absence of overt malignancy and are termed IgM-related disorders or more recently Monoclonal Gammopathy of Clinical Significance (MGCS). Treatment indication in these patients is dictated by the pathological characteristics of the circulating IgM rather than the tumour itself. The clinical workup and treatment options vary widely and differ from the regular treatment for WM. The aim of this review is to alert clinicians to IgM MGCS and to provide practical guidance of when to screen for these phenotypes. We discuss clinical characteristics, the underlying clonal profile, diagnostic workup and treatment considerations for five important subtypes: Cold agglutinin disease, type I and II cryoglobulinemia, IgM-associated peripheral neuropathy (PN), Schnitzler syndrome and IgM-associated AL Amyloidosis. The inhibition of the pathogenetic effects of the IgM has led to great success in cold agglutinin disease and Schnitzler syndrome, whereas the other treatments are centred on eradicating the underlying clone. Treatment approaches in cryoglobulinemia and PN are the least well developed. A multidisciplinary approach is required particularly for IgM-related neuropathies and Schnitzler syndrome. Future work exploring novel clone directed agents and pathogenetic IgM-directed therapies is welcomed.
Introduction

IgM monoclonal gammopathy of undetermined significance (MGUS) is defined by asymptomatic circulating IgM monoclonal (M) protein below 30 g/l with a lymphoplasmacytic bone marrow infiltration of less than 10% 1. IgM MGUS is a pre-malignant condition for non-Hodgkin lymphomas (NHL), mostly Waldenström macroglobulinemia (WM), chronic lymphocytic lymphoma (CLL), or plasma cell neoplasms. Most patients are candidates for observation. However, there is a proportion that develops diverse immunological and biochemical manifestations related to the monoclonal protein itself 2. This may lead to organ damage, even in the absence of overt malignancy. These so-called IgM-related disorders are a distinct clinical entity termed Monoclonal Gammopathy of Clinical Significance (MGCS) 3. The clinical workup and treatment options vary widely and differ from the regular treatment for WM which are outlined in recent consensus guidelines 4.

The aim of this review is to alert clinicians to IgM MGCS and to provide practical guidance of when to screen for these phenotypes. We discuss the clinical characteristics, diagnostic workup and treatment considerations for five important subtypes: cold agglutinin disease, cryoglobulinaemia, IgM-associated AL amyloidosis, IgM-related neuropathies and Schnitzler syndrome. A comprehensive list of IgM MGCS is listed below (table 1).

Clonal characterisation

It is important to identify the underlying clone as IgM MGUS may progress to a number of lymphoproliferative disorders or very rarely to myeloma5. IgM MGUS most commonly arises from a CD20+ lymphoplasmacytic cell without class-switching 1. The risk of progression to lymphoma, CLL, AL amyloidosis or multiple myeloma is 1.1 event per 100 person-years 5. In the largest series of 210 patients with IgM MGUS with a median follow up of 29.3 months, no patients progressed to IgM myeloma 5. The incidence and prevalence of IgM MGCS are unknown. Clonal B-cells in MGUS have the same genetic and molecular signature as the WM clone. However, MGUS cases have a significantly lower number of mutations than in
WM, indicating multiple genetic hits are required for progression. Somatic \textit{MYD88^{L265P}} mutation constitutently activates nuclear factor κB and triggers B cell proliferation. It is considered an early acquired mutation and is present in the majority of WM and IgM MGUS patients \cite{6,7}. The chemokine receptor CXCR4, a gene involved in homing of B cells in the bone marrow, is mutated (\textit{CXCR4\_MUT}) in a smaller proportion. This is usually subclonal and likely a late event. IgM myeloma has a distinct cell of origin, a pro-B cell, with frequent t(11;14), an absence of \textit{MYD88^{L265P}} mutation and higher expression of BCL2/BCL2L1 ratio \cite{8}. These clonal characteristics may have therapeutic implications. Table 2 summarises the data on the underlying histology and clonal characteristics of IgM MGCS compared with those seen in WM and IgM MGUS in general.
Primary cold agglutinin disease

Introduction

In primary cold agglutinin disease (CAD), autoimmune haemolytic anaemia is caused by a cold agglutinin that is a monoclonal IgMκ in >90% of cases, produced by clonal lymphocytes in the bone marrow. The antibody binds erythrocyte antigens (typically I) optimally at 4°C resulting in agglutination and classical complement pathway activation. The thermal amplitude describes the temperature width at which the antibodies are active, and only those with a thermal amplitude reaching higher than 28°C are considered pathogenetic. In most cases, complement activation is incomplete and extravascular haemolysis of C3b-opsonised erythrocytes occurs in the liver. Less frequently there is initiation of the terminal pathway, assembly of the membrane attack complex (C5b-C9) and intravascular haemolysis, which can lead to acute life-threatening anaemia. Cold agglutinins in the context of infection, autoimmune disease and overt lymphoma (including CLL, diffuse large B-cell lymphoma, WM) are referred to as cold agglutinin syndrome (CAS). Management of CAS is directed at treating the underlying cause and is not further discussed here.

Clinical characteristics

Patients present with chronic anaemia and/or cold-induced circulatory symptoms. Of 232 patients in an international retrospective case series, the median IgM was 3.2 g/l and over 90% had haemolytic anaemia and circulatory symptoms. Thirty-eight percent required transfusions at or before diagnosis and 47% during follow up. Around half had acrocyanosis or Raynaud’s syndrome affecting daily living. Ulcers or gangrene were rare (<2%). Haemoglobin is <80g/l in a third. Circulatory symptoms do not correlate with the degree of anaemia, nor bone marrow histology. There is an increased risk of thrombosis in CAD, likely related to intravascular haemolysis, which is not correlated with anaemia severity. CAD is a chronic disease with a 16-year estimated survival.
Clonality is demonstrated in approximately 80% of cases \(^{10,14}\) and the remainder likely require more sensitive methods to detect the pathogenic clone. The CAD clone has a distinct phenotype from WM. \(\text{MYD88}^{\text{L265P}}\) is rarely seen. Recurrent somatic mutation in \(\text{CXCR4}\) (20%) \(^{10,14,15}\), \(\text{KMT2D}\) (69%) and \(\text{CARD11}\) (31%) have been described \(^{16}\). Recurrent chromosomal abnormalities have been identified \(^{17}\). Based on 54 CAD bone marrow biopsies, “CAD-associated LPD” was defined, with typical morphology including absent plasmacytoid cells, universally restricted \(\text{IGHV4-34}\) gene usage and lack of \(\text{MYD88}^{\text{L265P}}\) \(^{14}\). Most patients meet MGUS criteria and extramedullary disease is rare \(^{10}\).

**Diagnostic workup**

Laboratory findings are consistent with haemolysis (which may include reticulocytosis, elevated lactate dehydrogenase, unconjugated hyperbilirubinaemia and decreased haptoglobin), monospecific direct antiglobulin test (DAT) strongly positive for C3d and a cold agglutinin titre of \(\geq 1:64\) at 4°C. Blood samples should be handled warm until separation to prevent agglutination.

**Treatment**

Treatment goals are to alleviate cold-induced symptoms and haemolytic anaemia. Response assessment should evaluate haemolytic activity, symptoms as well as clonal response. There are no standard criteria to assess response of cold-induced peripheral symptoms and instead clinicians depend on patient reported outcomes. A treatment algorithm is provided (figure 1, supplementary table 1). All patients should avoid cold exposure and be observed, particularly during periods of febrile illness and surgery \(^{10}\). Red blood cells should be transfused via a blood warmer. Symptomatic patients should commence use of folic acid and be considered for thromboprophylaxis. Importantly steroids and splenectomy are not effective in CAD \(^{9,12}\).

We recommend a frontline clone directed approach (figure 1), although achieving complete eradication is rare. The most established treatment is rituximab (R) based therapy.
Prospective trials of R-monotherapy show a modest response rate (RR) of 50% with rare complete response (CR) \(^1^8\). Real-world data show a 15-month median response duration and repeated responses in over a third of patients \(^1^0\). Efficacy is greatly improved with the addition of bendamustine (B). A prospective study of BR with a reduced dose of 70 mg/m\(^2\) bendamustine delivered for four cycles included 45 patients. Response rate was 71%, CR 40% and median increase of haemoglobin was 44 g/l. Grade 4 neutropenia was observed in 20% and 29% required dose reduction \(^1^9\). Updated data reported improved RR/CR rates due to deeper responses over time \(^1^0\). Rituximab-fludarabine is efficacious (RR 62%, CR 38%) but associated with an increased risk of secondary malignancy and is therefore not a preferred option \(^1^0,^2^0\). Bortezomib-based RR is 32% based on the prospective study of 19 patients \(^2^1\), although this was after only a single course of bortezomib. Bruton tyrosine kinase inhibitors (BTKis) were effective in all four treated patients with relapsed CAD in a retrospective report \(^2^2\). Daratumumab has been used in a case report \(^2^3\).

Clinical trials should be considered in relapsed disease. Promising studies have examined proximal complement inhibition to inhibit extravascular haemolysis. Complement inhibition necessitates indefinite treatment and fails to reduce vascular symptoms. A phase 3 study of anti-C1s, sutimlimab versus best supportive care rapidly halted haemolysis and in 73% transfusion independence, an increase in haemoglobin of over 15g/l and improved fatigue and is now FDA approved \(^2^4\). The effect of complement inhibition on thrombosis is not established, however D-dimer and thrombin-antithrombin complex levels decreased on treatment \(^1^3,^2^4\). Use of the C5 inhibitor eculizumab rapidly abrogates the terminal complement pathway with a short time to response. In the phase 2 trial however, there was a marginal haemoglobin rise of 8 g/l \(^1^3\). Proximal complement inhibition presumably, has greater effectiveness because it targets C3-mediated haemolysis via the liver that is often predominant in CAD. Ongoing clinical trials of complement inhibition in CAD include the C3b inhibitor, pegcetacoplan (phase 3, NCT05096403), Complement factor B inhibitor iptacopan.
Acute life-threatening intravascular haemolysis may necessitate transfusion. Plasma exchange (PEX) may be employed with all priming fluids and circuit apparatus pre-warmed and the replacement products run through a warmer. Erythropoietin support can be considered as erythropoietin can be inappropriately low in autoimmune haemolytic anaemia. Complement directed therapy may act as a bridge for R-combinations to target the underlying clone, which can take weeks to have an effect.
Cryoglobulinaemia

Introduction

Cryoglobulinaemia (CG) is characterised by immunoglobulins which precipitate at temperatures below 37°C and redissolve on warming. Monoclonal IgM can be associated with type I and type II CG. Type I CG consists of monoclonal immunoglobulins only. Type II “mixed” CG consist of monoclonal component possessing avidity for the polyclonal component of a different isotype (most frequently IgM with rheumatoid factor activity, the ability to bind to the Fc portion of IgG). Rheumatoid factor detected in type II CG is a monoclonal IgMκ in over 85% of cases. While most cases of type II CG are related to hepatitis C, we will focus on those related to monoclonal IgM.

Clinical characteristics

Data characterising patients with monoclonal IgM and CG are scant. Clinical characteristics are gleaned from retrospective cohorts grouping together IgG and IgM cases. The largest series reported over 1600 unselected CG patients. Nine percent had type I CG and 47% type II. The only series characterising IgM type I CG symptoms included 26 patients; 35% had underlying MGUS, 35% WM and 31% NHL. The incidence is likely underestimated as most literature reports are derived from centres not routinely screening for CG upon recognition of an IgM clone.

A wide spectrum of symptoms may be present (figure 1). Type I CG symptoms are defined by vascular occlusion and type II due to small and medium vessel vasculitis. Cutaneous involvement is most frequent in type I CG. Cutaneous manifestations range from purpura, livedo reticularis, acrocyanosis to cold urticaria, digital ischaemia, ulcers and necrosis. Of 26 patients, 46% had skin involvement, less than 10% had peripheral neuropathy (8%), arthralgia (8%) or renal involvement (4%). Other studies have reported peripheral neuropathy in a higher proportion of IgM cases, mainly sensory neuropathy (70%), but sensorimotor polyneuropathy and mononeuritis multiplex were also seen. Central nervous
system (CNS) involvement is rare unless due to hyperviscosity. No studies report specific presenting features of type II CG in those with circulating monoclonal IgM. In a mixed cohort of 203 type II patients with an underlying haematological disorder in 23%, skin manifestations predominated (85%). Compared to type I CG there was a greater proportion of peripheral neuropathy (56%), joint (41%), renal (38%), gastrointestinal (6%) and pulmonary (2%) involvement. Hyperviscosity is almost never seen.

**Diagnostic workup**

Laboratory testing is critical as a minimal amount of measurable cryoglobulin may cause symptoms. In one study where two-thirds were symptomatic, 58% of IgM type I CG cases demonstrated a cryocrit of <1%, which was a significantly greater proportion than in IgG CG. Symptoms do not correlate with the cryocrit and depend instead on the temperature at which precipitation occurs. Accurate detection of cryoglobulins requires samples to be taken into pre-warmed tubes which must not be allowed to cool below 37°C until the serum is separated, as the cryoglobulin may precipitate and not be detected. Similarly, a false-negative M-protein may result from the same process. In a French study, 9% of cases with negative results were positive on a follow-up test. Care must be taken with preanalytical variables; repeat testing of M-protein and cryoglobulins is indicated if the clinical suspicion is high. Increased plasma viscosity in the absence of a high IgM should trigger clinicians to consider CG.

A tissue biopsy may be indicated to identify renal or nerve involvement and distinguish from other causes. Intravascular precipitation of IgM triggered by cold exposure results in thrombotic obstruction and ischaemia in small vessels as evidenced on biopsy in type I CG. Leucocytoclastic vasculitis may be evident in type II.

**Treatment**

A treatment approach is outlined in figure 2. There is a paucity of data to guide optimal management. Mild symptoms may abate with cold prevention. Rapidly progressive
nephropathy and neuropathy have been reported at various stages of disease course, so careful monitoring is recommended. When CG is tested exclusively in symptomatic patients, treatment is commenced for CG-related symptoms in the majority (80%). Response assessment is not standardised and most focus on symptomatic improvement. Cryocrit at treatment initiation, change in cryocrit and time to nadir were predictive of symptom improvement in a mixed cohort of IgG and IgM type I CG. The underlying diagnosis of MGUS or lymphoma did not affect symptom improvement.

Treatment regimens are heterogeneous with small sample sizes. Plasma exchange may temporise critical symptoms and is utilised in up to a third of all CG in mixed cohorts; warming procedures should be in place. In the absence of robust evidence, definitive treatment should be directed at the underlying clone. Steroids are used in up to 90% of all CG (1 mg/kg), often together with immunosuppression. Rituximab combinations or bortezomib based treatment are typically employed with symptomatic responses in approximately 80%. Disappearance of cryoglobulin may be seen in half of patients. Transient disease exacerbation (‘IgM flare’) has been described following the use of rituximab in type I CG with low burden of disease (<10% infiltrate) and in type II CG. Some authors have suggested post-rituximab flare in type II CG may be due to the exogenous IgG from rituximab infusion that may also be a target of the monoclonal IgM. A study examining PEX prior to rituximab to prevent IgM flare is ongoing (NCT04692363). Currently there are no data on the use of autologous stem cell transplant (ASCT) or BTKi in IgM-associated CG.
IgM-associated AL Amyloidosis

Introduction

AL amyloidosis (AL) is a rare disorder caused by extracellular deposition of insoluble misfolded monoclonal light chain fragments as amyloid fibrils in tissues produced by an underlying plasma cell dyscrasia or lymphoma. IgM-associated amyloidosis accounts for 5 to 7% of all systemic amyloidosis. In non-IgM AL amyloidosis, advances in treatment have resulted in marked improvement in survival, yet patients with advanced disease have a poor outcome. Data on IgM-associated AL amyloidosis show no improvement over time.

Clinical characteristics

Due to its rarity, IgM-associated amyloidosis is less well characterised but increasingly recognised as a distinctive entity. When compared to non-IgM amyloidosis, patients are older with a history of MGUS or WM up to 65 months prior to diagnosis.

Multiple series indicate a smaller proportion of λ light chain involvement compared to non-IgM cases. Presenting free light chain (FLC) levels are lower that non-IgM AL; only two thirds had a difference between involved and uninvolved FLC of > 50mg/L in the largest study of 250 patients with IgM-associated amyloidosis. The pattern of organ involvement is also different, with a greater propensity for lymph node and soft tissue deposition (35%). Cardiac involvement is less common (45%) and neuropathy more frequent (28%).

Diagnostic workup

The exact nature of the clonal dyscrasia in IgM-associated AL amyloidosis remains unclear. The Mayo group has suggested a lymphoid predominant (LPL) or plasma cell predominant (pure plasma cell neoplasm; PPCN) type, based on morphology. Of 75 cases, the LPL type (63%) showed a higher tumour infiltrate, MYD88 L265P in 84%, CXCR4MUT in 29% but absent t(11;14), similar to WM. By contrast PPCN (23%) had similar rates of t(11;14) compared to non-IgM-associated amyloidosis and no MYD88 L265P/CXCR4MUT similar to IgM.
myeloma. PPCN appears to have poorer outcomes. These findings need independent confirmation to hone treatment approaches.

**Treatment**

There are no consensus guidelines, approved treatments or prospective clinical trials for IgM amyloidosis. The aims treatment are to reduce the clonal burden and improve performance status with a view to extending survival. A treatment algorithm is summarised in figure 3. Evidence is largely limited to retrospective series with heterogeneous regimens. Criteria developed for response assessment in non-IgM AL are applicable to IgM-associated AL with assessment of haematological response (HR) and organ response. Response assessment by both FLCs and M-protein had prognostic significance in retrospective series alongside age, Mayo stage, cardiac involvement, liver involvement and prior WM treatment. B2-microglobulin and lactate dehydrogenase do not independently affect survival, unlike in WM, which may relate to the low tumour burden. Despite lower cardiac involvement, IgM-associated amyloidosis does not have superior survival compared to non-IgM-associated amyloidosis, attributable to the inability to achieve deep clonal responses.

Induction of HR is more challenging with a reported 6-month overall RR of 39% vs 59% (p=0.008), deep RR are seen only in 24%. Organ RR are consequently poor (5% cardiac, 18% renal) and lower compared to a non-IgM-associated cohort.

Strategies to target the LPL and plasma cell clone have been employed. The best outcomes have been achieved by ASCT, with HR >90%. However, up to just 25% of all-comers were eligible for this intense therapy. The largest ASCT series of 38 patients included 58% with prior therapy and 100-day mortality was 5%. There was however a lower rate of cardiac involvement (26%), demonstrating the importance of patient selection. Induction chemotherapy prior to ASCT is not universally utilised. Conditioning most commonly involves
melphalan however the BEAM (carmustine-etoposide-cytarabine-melphalan) regimen has also been used \(^{44}\).

As the majority have an underlying LPL clone, induction therapy with rituximab-based combination chemotherapy is strongly preferred. In 27 cases, BR resulted in an intention-to-treat HR of 59% and CR 11% and median progression-free survival 34 months. 60% of patients treated with this combination in second line achieved a VGPR \(^{45}\). Bendamustine is neither neurotoxic nor cardiotoxic. Bortezomib in combination with rituximab and dexamethasone may provide rapid disease control. The only prospective trial recruited ten patients over one year \(^{46}\). HR was reached in 78% with sustained responses at a median of 11 months, after only two cycles. However, there were no complete responses. Thirty percent had treatment interruptions due to toxicity. Those with grade 3 sensory, and grade 1 painful neuropathy were excluded and treatment-related neuropathy is a particular concern in these patients. Disappointing responses have been found with frontline alkylating agents. In a series of 46 patients treated after 2003, HR was 37% and CR 0% \(^{41}\). Immunomodulatory drugs alone result in variable responses, mostly less than 50%. BTKis, although promising in WM, have been associated with low RR in IgM-associated amyloidosis. Of eight patients, only two achieved HR and median overall survival was nine months \(^{47}\). No studies have examined anti-CD38-bortezomib combinations, which is the standard of care in non-IgM AL amyloidosis \(^{48}\).

We consider upfront BR the treatment of choice in IgM-associated amyloidosis, consolidated with ASCT when performance status allows. In less fit patients, there is no consensus; treatment choices need to be individualised depending on affected organs and tolerance of treatments. Overall in this condition, deep responses remain poor. Future studies are required to address whether novel agent based regimes (including venetoclax, daratumumab and the newer BTKis) may lead to the progress in the outcomes of non-IgM AL amyloidosis.
**IgM-related neuropathies**

**Introduction**

IgM-related peripheral neuropathies (PN) encompass an array of entities including immune-mediated neuronal damage (such as anti-MAG) or direct neurotoxicity with infiltration by lymphoma (neurolymphomatosis), light chains (amyloidosis) or cryoglobulins. Peripheral neuropathy occurs in 15-30% of MGUS and WM cases, but the prevalence is likely affected by selection bias and variable neurological evaluation in patients as part of a workup of IgM M-protein. The UK registry reported 153 patients with IgM-related neuropathy, comprising anti-myelin-associated glycoprotein (MAG) neuropathy (55%), non-MAG IgM-neuropathy (35%) and less frequently (<4% each) AL amyloid, cryoglobulinemia, anti-ganglioside and chronic ataxic neuropathy, ophthalmoplegia, IgM M-protein, cold agglutinins and disialosyl ganglioside antibodies (CANOMAD) syndrome.

**Clinical characteristics**

Anti-MAG neuropathy is the most common and best-defined IgM-related neuropathy. Patients typically present with chronic-onset distal, symmetric neuropathy, sensory ataxia and tremor. Patients may be misdiagnosed as having chronic inflammatory demyelinating polyneuropathy (CIDP). It is important to correctly classify the neuropathy (table 3) as this has significant management implications. Atypical red flag symptoms not consistent with anti-MAG PN include acute onset, rapid tempo of symptoms, pain, dysautonomia, weight loss, cutaneous or CNS signs. These should alert the clinician to consider alternate diagnoses (figure 4). CANOMAD is a very rare chronic progressive syndrome associated with anti-ganglioside antibodies. This should be considered if there is sensory loss with ophthalmoplegia or ataxia. Bing-Neel syndrome is the term for CNS infiltration with LPL, with consensus guidelines published. Cryoglobulinaemia and amyloidosis are discussed in their respective sections.
Diagnostic workup

The majority of those with IgM-related neuropathy (> 90%) have symptoms at diagnosis of the underlying neurological disorder. This supports the strong need for careful early evaluation of patients jointly with an expert neurologist. The presence of a peripheral neuropathy alongside serum monoclonal IgM or anti-MAG antibody does not equal a causal relationship, since gammopathies as well as PN are both increasingly prevalent with age.

Patients should be tested for anti-MAG antibodies, but only high titre antibodies are clinically relevant in the presence of a characteristic clinical picture in anti-MAG neuropathy. A reduction in anti-MAG titres and levels of IgM M-protein with therapy appeared to correlate with improvement in neuropathy in a retrospective analysis of 50 studies. Responders also had a younger age of onset.

Nerve conduction tests and electromyography are warranted and characteristically show demyelination with reduced conduction velocity, disproportionately prolonged distal motor latency and absent sural potentials. Partial motor conduction block is rare. Progressive demyelination may result in secondary axonal loss which affects the likelihood of neural recovery. MRI imaging of the neuraxis and large volume CSF evaluation may be required if CNS involvement is suspected. A nerve biopsy may be needed if the diagnosis remains elusive despite systematic investigation. Comprehensive consensus guidelines provide further details.

Treatment

In general, in anti-MAG and non-anti-MAG neuropathy, treatment should be initiated only in those with significant or progressive disability. The aim of treatment is to halt progression and improve neurological function, although this may potentially take months to years, even after IgM responses. Although many neurological disability scales exist, they are not available outside of specialist neurology clinics and is no standardised response assessment. The use of serial validated patient-reported outcome scores (e.g. Inflammatory
Rasch-Built Overall Disability Scale) is advocated, as this can be easily undertaken in non-specialist clinics. An observational trial is currently recruiting with an aim to develop an IgM-specific disability scale (NCT03918421). Patients should be managed in a multidisciplinary fashion with input from neurology, haematology, physiotherapy and occupational therapy.

Rituximab is widely used in the setting of IgM-related neuropathies, but its use is inconsistent. A meta-analysis of rituximab demonstrated improvement in disability scales at eight to 12 months and long term efficacy is demonstrated in a third. Transient flare of symptoms with rituximab is observed in 12% in the largest series. Steroids, IVIG and PEX alone do not provide long term clinical benefit in anti-MAG neuropathy and are resource-intense respectively. In CANOMAD IVIg and R-based regimens are effective (53% and 52% >PR, respectively) while CIDP is responsive to IVIg, highlighting the relevance of correct diagnostic classification.

Although data are largely limited to retrospective series, targeting the underlying clone is feasible in IgM-related neuropathy; the optimum depth of response is unknown. Clinical improvement or stabilisation is significantly more likely with R-containing therapy (Dexamethasone, Rituximab, Cyclophosphamide; BR; Cyclophosphamide, Prednisolone, Rituximab, Vincristine), non-amyloid related neuropathy and attainment of at least partial response.

There is an unmet need for reliable biomarkers for diagnosis, appropriate selection of patients for treatment and monitoring response. There is a lack of prospective clinical trials to optimise treatment options. A phase 2 clinical trial, MAGNAZ, of the oral BTKi zanubrutinib in anti-MAG PN is underway.
Schnitzler syndrome

Introduction

Schnitzler syndrome is a rare autoinflammatory disorder characterised by an IgM monoclonal gammopathy and chronic recurrent urticarial rash. The Strasbourg criteria outline additional minor criteria of recurrent fever, abnormal bone remodelling with or without bone pain, neutrophilic dermal infiltrate, leucocytosis or elevated C-reactive protein. Around 300 cases have been reported to date. It is underdiagnosed and despite its rarity, is important to identify as specific treatment can significantly improve quality of life.

Clinical characteristics

Of 281 cases in the largest case series, fever was present in 72%, anaemia 63%, arthralgia 68%, bone pain 55%, lymphadenopathy 26%, and less than 10% liver or spleen enlargement and neuropathy. Smaller series reported up to around 50% fatigue and weight loss. The urticarial rash can cover any part of the body, but face, palm and sole involvement is infrequent, as is intense pruritis. Skin lesions typically resolve within hours. The time from onset of symptoms to diagnosis is prolonged, at a median of five years and may be as long as 20 years.

The monoclonal gammopathy is almost always IgMk. Bone marrow involvement is minimal, around 4% in one series and a median M-protein of 0.6 g/dL has been observed. In a large case-series, sixty-three percent of 281 bone marrow samples were reported as normal. Peripheral blood MYD88<sup>L265P</sup> has been detected in 30% of 30 patients. The authors suggest this may correlate with WM risk, although this may be an underestimate as the sensitivity of detecting peripheral blood B-cell clones may be hampered in low-level disease burden. Bone marrow MYD88<sup>L265P</sup> frequency has not been studied. Chronic inflammation may lead to AA amyloidosis in 2%. At a median of 8 years, the rate of evolution to lymphoma is 20%, which is in line with progression in unselected IgM MGUS cohorts.
Schnitzler syndrome is associated with cytokine dysregulation. It bears close phenotypic resemblance to the inherited disorder, cryopyrin-associated periodic syndrome, caused by gain-of-function mutations in the \textit{NLRP3} gene. This results in upregulation of interleukin-1\(\beta\) (IL-1\(\beta\)) production and has informed therapeutic options in Schnitzler syndrome, by targeting IL-1\(\beta\).

**Diagnostic workup**

There is no single diagnostic test and the diagnosis is made based on clinical characteristics. Differentials for the rash and fever include adult-onset Still's disease, systemic lupus erythematosus, acquired C1 esterase deficiency, cryopyrinopathies and CG (cold-induced urticaria). Skin biopsy reveals a neutrophilic urticarial dermatosis without features of vasculitis.

**Treatment**

Treatment is aimed at reducing the considerable associated morbidity related to rash, fever and joint and bone pain. Symptoms respond poorly to historic first line agents including antihistamines, nonsteroidal anti-inflammatory drugs, dapsone and colchicine. Use of high-dose steroids, although moderately effective, is limited by long-term toxicities.

Without anti-IL treatment, morbidity is high. In a series of 21 patients, all had almost daily symptoms with a profound effect on their quality of life. Anti-IL-1 agents anakinra, canakinumab, and rilonacept have all been used but not directly compared. Anakinra, a recombinant IL-1-receptor antagonist, is the treatment of choice with the greatest experience and efficacy (94% efficacy in 86 cases), with durable responses (83% CR after a median of 36 months). Anakinra has a half-life \((t_{1/2})\) of 4-6 hours with impressive control of all signs within hours, normalisation of C-Reactive protein and abrogation of AA amyloidosis risk. Nonetheless, patients require continuous daily injections and relapse post discontinuation occurs. Canakinumab, an IL-1\(\beta\) monoclonal antibody, is long-acting \((t_{1/2} 21-28\text{ days})\) and thus administered less frequently. Phase 2 placebo-controlled randomised data
demonstrates efficacy. For seventeen patients on the long-term study, clinical efficacy was highest when patients injected canakinumab as needed. A systematic review of 34 patients showed CR in 59% 68. Rilonacept, IL-1 binding and neutralising fusion protein, achieves near CR in 50% 69. Tocilizumab, an IL-6 receptor antagonist, has been beneficial in three patients who were refractory to anakinra 70.

Cyclophosphamide, rituximab and ibrutinib have achieved responses when treatment was given for overt lymphoma but largely ineffective or untested in the absence of lymphoma 65. There is little to support the notion that anti-IL therapy affects the underlying B-cell clone.
Conclusion

We have discussed a range of distinctive entities of IgM MGCS, including their specific clinical characteristics, underlying clonal profile, diagnostic workup and treatment considerations. Careful evaluation of the presenting features and thorough interrogation of the underlying clone is critical. Determining the nature of either a mature B-cell derive clone or plasma cell clone will have management implications. There is an IgMκ predominance in all cases except IgM-associated AL amyloidosis. Treatment indication is dictated by the pathological characteristics of the circulating IgM rather than the tumour itself. While deep suppression of the pathogenic IgM is typically required for response, achieving long-term clonal eradication is challenging, as demonstrated by low CR rates. Treatment inhibiting the pathogenetic effects of IgM whilst not directed at the underlying clone has led to great success in CAD (complement inhibitors) and Schnitzler syndrome (cytokine inhibition), whereas the other treatments are centred on eradicating the underlying clone. Treatment approaches in CG and PN are the least well developed. A multidisciplinary approach is required particularly for IgM-related neuropathies and Schnitzler syndrome.

Due to their rarity, data are scant and collaborative research is imperative to aid defining optimal treatment strategies for IgM MGCS. International registries may better define characteristics and assess treatment outcomes. Future work exploring clone directed treatment options and pathogenetic IgM-directed therapies is welcomed.
References


Table 1. List of IgM MGCS

<table>
<thead>
<tr>
<th>IgM MGCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cold agglutinin disease*</td>
</tr>
<tr>
<td>• Type 1 and 2 cryoglobulinaemia*</td>
</tr>
<tr>
<td>• IgM-related neuropathies (including anti-MAG peripheral neuropathy*, non-MAG peripheral neuropathy, antiganglioside neuropathies, chronic ataxic neuropathies with disialosyl antibodies)</td>
</tr>
<tr>
<td>• IgM-associated AL amyloidosis*</td>
</tr>
<tr>
<td>• Schnitzler syndrome*</td>
</tr>
<tr>
<td>• Monoclonal gammopathy of renal significance (including immunoglobulin deposition disease, light chain proximal tubulopathy, proliferative glomerulonephritis with monoclonal immunoglobulin deposits)</td>
</tr>
<tr>
<td>• Acquired von Willebrand’s syndrome and other coagulation factor deficiencies</td>
</tr>
<tr>
<td>• Acquired C1 inhibitor deficiency</td>
</tr>
<tr>
<td>• Pure red cell aplasia</td>
</tr>
<tr>
<td>• IgM POEMS</td>
</tr>
</tbody>
</table>

*These entities are discussed in further detail in this review.
Table 2. Clonal characteristics of IgM MGCS, MGUS and WM.

<table>
<thead>
<tr>
<th></th>
<th>IgM MGUS</th>
<th>WM</th>
<th>Cold agglutinin disease</th>
<th>Cryoglobulinaemia</th>
<th>IgM AL amyloidosis</th>
<th>Anti-MAG neuropathy</th>
<th>Schnitzler syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGUS (&lt;10% infiltration)</td>
<td>100%</td>
<td>0%</td>
<td>70%</td>
<td>Type I:</td>
<td>27%</td>
<td>60%</td>
<td>73%</td>
</tr>
<tr>
<td>WM (&gt;10% infiltration)</td>
<td>0%</td>
<td>100%</td>
<td>7%</td>
<td>30-40%, 30-40%,</td>
<td>54%</td>
<td>35%</td>
<td>13%</td>
</tr>
<tr>
<td>Other</td>
<td>24%</td>
<td>71%</td>
<td>20-30%, 27,30</td>
<td>Type 2: not reported</td>
<td>19%</td>
<td>8% 72,73</td>
<td>15% 63</td>
</tr>
<tr>
<td><strong>IgM light chain restriction</strong></td>
<td></td>
<td></td>
<td></td>
<td>71% 75% 100%</td>
<td>IgMκ 85% type I</td>
<td>IgMκ 60% 40%</td>
<td>IgMκ 81% 91%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IgMκ 77% type II</td>
<td>IgMκ 77% type II</td>
<td>IgMκ 77% type II</td>
<td>IgMκ 77% type II</td>
</tr>
<tr>
<td><strong>Molecular studies in bone marrow</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYD88&lt;sup&gt;L265P&lt;/sup&gt;</td>
<td>Up to 80%</td>
<td>&gt;90%</td>
<td>0%</td>
<td>Not reported*</td>
<td>58%</td>
<td>73%</td>
<td>Not reported***</td>
</tr>
<tr>
<td>CXCR4&lt;sup&gt;MUT&lt;/sup&gt;</td>
<td>5%</td>
<td>40%</td>
<td>22% 15</td>
<td>Not reported</td>
<td>17% 38**</td>
<td>12% 72</td>
<td>Not reported***</td>
</tr>
<tr>
<td>IGHV/IGLV gene usage</td>
<td>VH3</td>
<td>VH3</td>
<td>VH4-34</td>
<td>Not reported</td>
<td>LV2</td>
<td>VH4-34</td>
<td>VH3</td>
</tr>
</tbody>
</table>

*MYD88<sup>L265P</sup> reported in 92% of WM associated type I cryoglobulinaemia<sup>76</sup>

**these mutations are not seen in pure plasma cell neoplasm (PPCN) subtype

***30% in peripheral blood<sup>66</sup>
### Table 3. Features of IgM and non-IgM-related neuropathies

<table>
<thead>
<tr>
<th></th>
<th>Non-IgM-related</th>
<th>IgM-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIDP</td>
<td>Theray</td>
<td>POEMS</td>
</tr>
<tr>
<td></td>
<td>related</td>
<td></td>
</tr>
<tr>
<td>Onset</td>
<td>Gradually</td>
<td>Gradually</td>
</tr>
<tr>
<td></td>
<td>relapsing</td>
<td>progressive</td>
</tr>
<tr>
<td></td>
<td>emergent</td>
<td></td>
</tr>
<tr>
<td>Symmetrical, proximal,</td>
<td>Symmetrical,</td>
<td>Symmetrical,</td>
</tr>
<tr>
<td>sensory and motor</td>
<td>distal,</td>
<td>sensory,</td>
</tr>
<tr>
<td></td>
<td>progressive</td>
<td>may be</td>
</tr>
<tr>
<td>Demyelinating/Axonal</td>
<td>Demyelinating</td>
<td>painful</td>
</tr>
<tr>
<td>Supportive tests</td>
<td>Conduction</td>
<td>Clinical</td>
</tr>
<tr>
<td></td>
<td>block and</td>
<td>features are</td>
</tr>
<tr>
<td></td>
<td>abnormal</td>
<td>key (see CG</td>
</tr>
<tr>
<td></td>
<td>temporal</td>
<td>section)</td>
</tr>
<tr>
<td></td>
<td>dispersion</td>
<td></td>
</tr>
<tr>
<td>Light chain predominance</td>
<td>Not IgM</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>associated</td>
<td>IgMκ 85%</td>
</tr>
<tr>
<td></td>
<td>Not IgM</td>
<td>type I</td>
</tr>
<tr>
<td></td>
<td>associated</td>
<td>IgMκ 77%</td>
</tr>
<tr>
<td></td>
<td>Not reported</td>
<td>type II</td>
</tr>
<tr>
<td></td>
<td>IgMκ 84%</td>
<td></td>
</tr>
</tbody>
</table>

*Red flag features
Figure 1 legend: Management of CAD
Key: CAS, cold agglutinin syndrome; EPO, erythropoietin

Figure 2 legend: Management of cryoglobulinaemia
*Virology testing includes full Hepatitis B profile, Hepatitis C, HIV

**Emergency indications include symptomatic hyperviscosity, critical ischaemia, severe neuropathy, progressive renal impairment

Key: NCS/EMG, nerve conduction studies, electromyography, uPCR, urine protein creatinine ratio.

Figure 3 legend: Management of IgM-associated amyloidosis
R-Bendamustine, Rituximab-Bendamustine; BEAM, carmustine etoposide cytarabine melphalan; Mel, melphalan; SFLC, serum free light chains

*Histological assessment includes targeting affecting organ, consider abdominal fat biopsy. Exclude other acquired and hereditary amyloidosis

** Organ assessment includes comprehensive evaluation of organs including cardiac, renal, neurological, gastrointestinal and soft tissue involvement.

Figure 4 legend: Management of IgM-related neuropathies
Key: NCS/EMG;

*nerve biopsy after consultation with expert neurologist, in selected cases only
Cold Agglutinin Disease
IgM M-protein + DAT C3d + CA titre >1:64

Exclude secondary CAS

Symptom assessment

Symptomatic
Folic acid, consider thromboprophylaxis
Avoid cold exposure

Asymptomatic
Observe
Avoid cold exposure

Clonal assessment:
CT, Bone marrow studies, flow cytometry, MYD88 (CXCR4)

Monitor reticulocyte count, LDH, unconjugated bilirubin, haptoglobin

Emergency
Plasma exchange, warmed red cell transfusion
Consider EPO, complement inhibition

Frontline
Clone directed
Rituximab, BR, Clinical trials

At relapse: consider repeat clonal assessment

Response assessment:
Clinical symptoms, haemoglobin, haemolysis markers

Relapse
Clone directed
Consider clinical trials, BR, Bortezomib, Daratumumab, BTKi

Complement directed
Complement inhibition clinical trials
IgM M-protein + Type I or II Cryoglobulinaemia

Symptom assessment

**Skin:** purpura, livedo reticularis, acrocyanosis, cold urticaria, distal ischaemia, ulcers, necrosis
**Neurological:** peripheral neuropathy
**Renal:** glomerulonephritis, nephrotic syndrome
**Hyperviscosity:** bleeding, visual disturbance, headache, CNS ischaemia
**Musculoskeletal:** Myalgia, arthralgia, arthritis
**Gastrointestinal/pulmonary/cardiac:** rare (type II)

**Prior to treatment:** Cryocrit, Bone marrow biopsy, CT, C3,C4,RF,virology (type II)*

**Treatment**
- Avoidance of cold exposure
- Antiplatelet/anticoagulation for ischaemic events
- **Emergency**: Plasma exchange, steroids
  - Rituximab, BR, DRC, BTKi, Clinical trials

**Disease and symptom burden assessment**

**Observe**
- Avoidance of cold exposure

**Consider:**
- NCS/EMG, uPCR,
- autoimmune screen (type II)
- Biopsy (skin, nerve, renal)

**Response assessment:**
- Clinical symptoms, Cryocrit
AL amyloidosis with IgM M-protein

Standard work-up:
- Histology*
- SPEP/SFLC
- Organ assessment**

Bone marrow studies
- Flow cytometry, t(11;14), MYD88, CXCR4 status

LPL (majority) or no infiltrate
- CT or PET/MRI

PCCN (minority)

Consider clinical trials

**Frontline**
- R-Bendamustine (alternative bortezomib based)
- BEAM or Mel ASCT consolidation for suitable patients
- Consider treatment as per non-IgM AL

**Relapse**
- Frontline options, Cyclophosphamide-based, Clinical trials
- Treat as per relapse non-IgM AL

*Response assessment:
- HR (SFLC, paraprotein)
- Organ response
Acute onset (<6 months), rapid progression, pain, dysautonomia, weight loss, cutaneous signs or CNS signs

Exclude non-IgM causes: Vitamin B12, HbA1c, HIV. Therapy related neuropathy, CIDP

IgM + Neuropathy

Red flag symptoms?

Yes

AL amyloidosis
Cryoglobulinemia
Bing-Neel Syndrome
Neurolymphomatosis

No

Perform anti-MAG/ganglioside Ab, NCS/EMG, consider MRI, CSF, nerve biopsy *

IgM-related neuropathy

Anti-MAG neuropathy

Non Anti-MAG neuropathy

CANOMAD

POEMS syndrome

Small fibre neuropathy

Neurological disability and clonal assessment

Significant neurological disability

Consider IVIG, rituximab

Treat as per POEMS

No clone directed treatment

Rituximab, BR, DRC, Clinical trials
## Supplementary data

### Supplementary table 1. Summary of CAD treatment considerations

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Target</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frontline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab (R)</td>
<td>LPL</td>
<td>Time of onset is weeks 375mg/m² for 4 weeks</td>
</tr>
<tr>
<td>R-Bendamustine</td>
<td>LPL</td>
<td>Consider if fit, 4 cycles</td>
</tr>
<tr>
<td>R-Fludarabine</td>
<td>LPL</td>
<td>Risk of secondary malignancy, so only selectively use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Target</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relapse/Novel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib + R</td>
<td>LPL/Plasma cell</td>
<td>1.3 mg/m² subcutaneous, caution dose in those with neuropathy</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>LPL</td>
<td>Case report use 23</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>LPL/Plasma cell</td>
<td>Case report use 24, 16 mg/kg weekly (weeks 1-6), 2-weekly (weeks 9-24) and 4-weekly thereafter</td>
</tr>
<tr>
<td>Eculuzimab (C5 inhibitor)</td>
<td>Complement</td>
<td>Time of onset is days, may be useful in acute severe intravascular haemolysis. No effect on extravascular haemolysis</td>
</tr>
<tr>
<td>Sutimlimab (C1s inhibitor)</td>
<td>Complement</td>
<td>Phase 3 open-label, single arm (NCT03347396, CARDINAL), completed recruitment Phase 3 randomised placebo-controlled clinical trial (CADENZA, NCT03347422)</td>
</tr>
<tr>
<td>Pegcetacoplan (C3b inhibitor)</td>
<td>Complement</td>
<td>Phase 3 clinical trial (NCT05096403) for those received prior Rituximab. Twice-weekly subcutaneous 1080-mg vs placebo</td>
</tr>
<tr>
<td>Iptacopan (Complement factor B inhibitor)</td>
<td>Complement</td>
<td>Phase 2 clinical trial (NCT05086744) for relapsed patients. 200mg capsule BD</td>
</tr>
<tr>
<td>Cinryze (C1 esterase inhibitor)</td>
<td>Complement</td>
<td>Phase 2 clinical trial (2012-003710-13/NL)</td>
</tr>
</tbody>
</table>