During routine checks or when investigating the causes of an increased erythrocyte sedimentation rate, especially in older people a spike-like peak can sometimes be observed in the gamma fraction of the serum protein electrophoresis. This “M gradient” is a sign of a monoclonal gammopathy, whose cause will have to be investigated (diagram).

Multiple myeloma is the best known disorder associated with monoclonal gammopathy, but not the most common one. Most common is monoclonal gammopathy of undetermined significance (MGUS). This is found in more than 3% of people older than 70, often as an incidental finding. Many other diseases or disorders with sometimes complex pathophysiology and effects on multiple organ systems – such as the nervous system, kidneys, heart, bones, and blood formation – may also be a cause for this laboratory result (box 1).

In this review article, we show the differential diagnosis of IgM gammopathy and its multiple implications for clinical practice, on the basis of a selective literature review and our own research and study data.

Differential diagnosis

When an M gradient is first found on serum protein electrophoresis, serum and urine immune fixation electrophoresis should be performed additionally to confirm the diagnosis of monoclonal gammopathy, and the class specific immunoglobulins should be quantitatively determined. The immunoglobulin isotype can be determined simultaneously, i.e., monoclonal IgG, IgA, or IgM, or the corresponding light chain κ or λ (diagram). Immune fixation electrophoresis is required only for the primary diagnosis and possibly for checking whether the treatment has been successful. Quantitative measuring of free light chains in the serum is a new, highly sensitive, method that may be helpful in assessing the prognosis and controlling the course of the disease. The most important differential diagnosis of IgM gammopathy is monoclonal gammopathy of undetermined significance (MGUS) of the
IgM type. To distinguish this finding from the lymphoproliferative disorders described below, a bone marrow biopsy and ultrasonography of the upper abdomen are required. Additionally, a detailed medical history and physical examination are indicated, during which particular attention should be paid to enlarged lymph nodes, an enlarged spleen, and ostalgia. X-ray investigation of the skeleton including the large tubular bones is usually not required and should be considered only when bone involvement is suspected, for example in ostalgia. A diagnosis of MGUS can be made only if no pathological findings are confirmed during this procedure (box 2).

An important differential diagnosis comprises the so called "IgM-associated disorders." Asymptomatic and symptomatic Waldenström's macroglobulinemia (WM) (table 1) have to be differentiated. For a diagnosis of WM, the following are required:

- A confirmed finding of monoclonal IgM at any concentration
- Bone marrow infiltration by small lymphocytes with plasmocytoid differentiation or plasma cell differentiation
- Inter trabecular pattern of bone marrow
- The characteristic immunophenotype of lymphocytes in the bone marrow.

The differentiation from the "lymphocytoid" variant of chronic lymphatic leukemia (CLL) may occasionally present difficulties; however, unlike WM, this is positive for CD5 and CD23.

Further, rarer differential diagnosis of monoclonal IgM gammopathy are marginal zone lymphoma (MZL) – including the mucosa-associated and splenic subtypes (mostly CD11c

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**BOX 1**

**Possible causes of monoclonal gammopathy type IgM**

- Monoclonal gammopathy of undetermined significance (MGUS)
- IgM-associated disorders (e.g. cryoglobulinemia, cold agglutinin-induced hemolytic anemia, peripheral neuropathies)
- Waldenström's macroglobulinemia
- Marginal zone lymphoma
- Other indolent lymphomas (mantle cell lymphoma, CLL, follicular lymphoma, IgM myeloma)

**BOX 2**

**Gammopathy of undetermined significance (MGUS) (1)**

- Serum concentration of monoclonal immunoglobulin ≤ 30 g/l
- No osteolysis
- No anemia
- No hypercalcemia or renal insufficiency that is associated with monoclonal plasma cell proliferation
- ≤ 10% plasma cells in the bone marrow
positive) – and other B-cell lymphomas, such as mantle cell lymphoma and follicular lymphoma. Since the histological examination of the bone marrow in WM patients typically reveals a high proportion of plasma cells, a differentiation will sometimes have to be made from the rare IgM myeloma. Immunohistologically, IgM myeloma often shows expression of CD138 or cyclin D1; further, a finding of osteolytes enables a differential diagnosis.

**Monoclonal gammopathy of undetermined significance**

Monoclonal gammopathy of undetermined significance, which is often an incidental finding, mostly of the immunoglobulin isotope IgG, more rarely IgA or IgM, is a premalignant pre-stage of multiple myeloma or other lymphoproliferative disorders. Its incidence increases with age. According to a recent study in the United States, 3.2% of people older than 50 and 5.3% of those older than 70 have monoclonal gammopathy of undetermined significance (MGUS) (1). The isotype IgG occurs in 68.9% of such patients, IgA in 17.2%, and IgM in 10.8%. The patients are asymptomatic, as per definition, and usually have a monoclonal IgM concentration below 30 g/l, hemoglobin measurement of more than 12 g/dl, and an absence of bone marrow infiltration due to lymphoma (2). The rate of progression of MGUS of any isotype into a multiple myeloma or another lymphoproliferative disorder is 1% per year.

**IgM-associated disorders**

In patients with an IgM-associated disorder, monoclonal IgM is found as well as the associated symptoms – e.g., polynuropathy, cryoglobulinemia, and other autoimmune phenomena – but no lymphoma infiltration of the bone marrow. Cryoglobulins are immunoglobulins that precipitate in the cold; they are associated with a range of infectious, autoimmune, and tumor disorders. The association of essential mixed cryoglobulin type II with HCV infection in 80–90% of cases is well known. The most common IgM-associated disorders include immunologically mediated disorders, such as cold agglutinin-induced hemolytic anemia and the peripheral neuropathies. Responsible are the autoantibody activity of monoclonal IgM against glycoproteins and glycolipids of the peripheral nerves. The most common form is distal symmetrical chronic demyelinating peripheral neuropathy (3).

IgM can be deposited directly in tissue, e.g., the renal glomerula, and may thus result in glomerular damage with proteinuria, dehydration, and uremia. Independent of the level of the monoclonal protein concentration, amyloidosis due to light chain deposits may be caused. Additionally, in different rheumatic disorders, in Aids, or after organ transplantation, secondary monoclonal IgM gammopathies may develop that can result in organ damage in the way described.

**Waldenström’s macroglobulinemia**

In 1944, Jan Gostar Waldenström, a Swedish specialist in internal medicine, described a clinical picture in 2 patients that was characterized by fatigue, nosebleeds, swollen lymph nodes, severe anemia, low serum fibrinogen levels, and high blood viscosity. In these patients, an abnormal high molecular serum protein level was confirmed, which was later found to be monoclonal IgM (4).
The terms Waldenström’s disease or Waldenström’s macroglobulinemia have subsequently been used for many lymphatic neoplasias that are characterized by monoclonal IgM. In the current WHO classification, WM is grouped with lymphoplasmocytic lymphoma and termed “lymphoplasmocytic lymphoma/Waldenström’s macroglobulinemia.” The mere confirmation of monoclonal IgM production does not automatically equate to WM, because this abnormality can occur in several other B-cell lymphomas and in MGUS. The term WM as an independent clinical-pathological entity should be used only in patients with histologically proved lymphoplasmocytic lymphoma – defined as per the WHO classification – in whom monoclonal IgM protein has been found concomitantly (consensus recommendation, 2nd IWWM, 2002, Athens [13]).
WM is a rare disorder. In the US, the estimated prevalence is 1,500 newly diagnosed cases per year (5). In several large cohorts of patients, a median age of 63 has been described, as well as a slight predominance of the disorder in men (5). Familial clustering has been described in individual cases; which implies a certain genetic predisposition. The presenting symptoms of WM are due to direct tumor formation on the one hand, and to the specific characteristics of monoclonal IgM on the other hand. Usually, IgM results in a strongly increased erythrocyte sedimentation rate.

In addition to bone marrow infiltration (figure 1) with subsequent hematopoietic insufficiency, splenomegaly is the primary presenting symptom. In its progressive stages it may lead to abdominal pain in many patients, but also – in the sense of hypersplenism – to cytopenia (figure 2). However, excessive lymphadenopathy, as found in other entities, is rare. Practically every organ system may be affected by direct infiltration or paraneoplastic processes.

Circulating IgM molecules in the form of aggregates and due to hydropexia may result in increased osmotic pressure and a decreased flow rate, in turn resulting in disrupted microcirculation (hyperviscosity syndrome). In some 20% of patients, agglutination of the IgM molecules at low temperatures can be observed (type I cryoglobulinemia). Up to 20% of patients with WM develop IgM-associated peripheral neuropathy. Of practical relevance is the observation that when IgM measurements and blood viscosity are very high, and the plasma volume subsequently expanded, Hb measurements may be falsely low. In this situation, erythrocyte concentrates should be transfused only hesitantly as they increase the blood viscosity further.

**Prognosis in IgM MGUS and WM**

A current study of 213 patients with IgM gammopathy in the US (Olmsted Country, Minnesota) found the mean age at diagnosis of gammopathy to be 74. The likelihood of a transformation into a lymphoproliferative malignant disorder was 10% after 5 years, 18% after 10 years, and 24% after 15 years. The resulting transformation rate was 1.5% per year, which is higher than that of MGUS in other isotypes. Seventeen patients developed non-Hodgkin’s lymphoma, 6 patients WM, 3 patients primary amyloidosis, and 3 patients chronic lymphocytic leukemia (6). In patients with a high IgM serum level at first diagnosis (>25 g/l) and a low serum albumin level, the risk of malignant transformation was higher. The probability of a patient dying of a lymphoproliferative disorder at old age was much lower than for other causes of death – e.g., cardiovascular or cerebrovascular disorders.

**TABLE 2**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Treatment</th>
<th>Evidence level</th>
<th>Bibliographical reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM MGUS</td>
<td>No therapy, watchful waiting</td>
<td>IIb</td>
<td>(1, 2)</td>
</tr>
<tr>
<td>IgM-associated disorders (e.g., polyneuropathy)</td>
<td>Chemotherapy, Rituximab</td>
<td>III</td>
<td>(61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(19, e2–e5)</td>
</tr>
<tr>
<td>Waldenström’s disease</td>
<td>No treatment, watchful waiting</td>
<td>IIb</td>
<td>(7, 8)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Chlorambucil</td>
<td>Ila</td>
<td>(14)</td>
</tr>
<tr>
<td></td>
<td>Purine analogues (F, CI)</td>
<td>Ila</td>
<td>(66, e7)</td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
<td>Ila</td>
<td>(15–17)</td>
</tr>
<tr>
<td></td>
<td>Purine analogue combination (e.g., PC-R)</td>
<td>Ila</td>
<td>(20, e8)</td>
</tr>
<tr>
<td>With indication for therapy*</td>
<td>Other combinations (e.g., R-CHOP)</td>
<td>Ila</td>
<td>(21, e9)</td>
</tr>
<tr>
<td></td>
<td>Autologous/allogenic stem cell transplant</td>
<td>Ila</td>
<td>(23, e10, e11)</td>
</tr>
</tbody>
</table>

MGUS, monoclonal gammopathy of undetermined significance; F, fludarabine; CI, cladribine, PC-R, pentostatin-cyclophosphamide-rituximab; R-CHOP, rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone.

*See box 3
The life expectancy of patients with WM is comparable to that of patients with other indolent lymphomas. With or without therapy, the mean survival is 5 to 10 years. All larger studies found in agreement that age over 60 and a low hemoglobin level below 10 g/dl are unfavorable prognostic variables (7–10). The level of IgM paraprotein does not allow conclusions about the prognosis in the individual case. Patients with IgM-MGUS, asymptomatic or “smoldering” WM often remain stable for years, even without treatment. At least 20% of patients with WM survive beyond 10 years; 10–20% die due to other causes (8, 11, 12).

**Treatment**

Patients with IgM-MGUS as a rule do not require treatment. But because of the enduring risk of transformation into a lymphoproliferative malignancy, unlimited annual follow-up of the laboratory variables and the physical condition are advisable. Patients with IgM-associated disorders, e.g., peripheral neuropathy, may benefit from treatment with rituximab. Individual observations confirm this (table 2).

As in all indolent B-cell lymphomas, asymptomatic patients with WM do not require treatment. The consensus recommendations of the 2nd IWWM for therapy indications are listed in box 3 (13).

**Plasmapheresis**

Plasmapheresis can be used to lower effectively the serum level of circulating IgM. This complex procedure is rarely necessary, however. It is indicated in patients with a very high IgM measurement and life threatening symptoms caused by hyperviscosity, e.g., severe bleeds, visual impairment, vertigo, ataxia, impaired consciousness. The effects of plasmapheresis are short lasting.

**Chemotherapy**

Alkylation agents as well as purine analogues and the monoclonal anti-CD20 antibody rituximab have been found to be effective in the primary treatment of WM (table 2). Thus far, no comparative studies have been done that would justify the preferential use of one of these substances.

**Alkylation agents**

Until recently, alkylation agents were regarded as standard treatment. As a rule, chlorambucil was given orally. Partial remission can be achieved in 50–70% of cases with chlorambucil (14). Complete remission is rare. The extent to which more aggressive combination regimens containing alkylation agents, such as the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisolone), may be superior to chlorambucil monotherapy has so far not been investigated in comparative studies. Especially in older patients, chlorambucil is therefore still a well tolerated and cost effective therapeutic option.

<table>
<thead>
<tr>
<th>BOX 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications for therapy in Waldenström’s disease</strong></td>
</tr>
<tr>
<td>- Constitutional symptoms, such as sustained fever, strong night sweats, fatigue as a result of anemia, weight loss</td>
</tr>
<tr>
<td>- Progressive symptomatic lymphadenopathy or splenomegaly</td>
</tr>
<tr>
<td>- Anemia with hemoglobin levels &lt;10 g/dl subsequent to bone marrow infiltration</td>
</tr>
<tr>
<td>- Thrombopenia &lt;100/nl subsequent to bone marrow infiltration</td>
</tr>
<tr>
<td>- Hyperviscosity syndrome</td>
</tr>
<tr>
<td>- Symptomatic sensorimotor peripheral neuropathy</td>
</tr>
<tr>
<td>- Systemic amyloidosis</td>
</tr>
<tr>
<td>- Renal insufficiency</td>
</tr>
<tr>
<td>- Symptomatic cryoglobulinemia</td>
</tr>
</tbody>
</table>

Recommendations of the consensus panel of the 2nd International Workshop on Waldenström’s macroglobulinemia, Athens 2002 (13)
Purine analogues
For 15 years now, purine analogues, such as fludarabine, cladribine, and pentostatin, have been used in diverse lymphoproliferative disorders including WM. Treatment response rates of 40–90% were achieved (e6, e7).

Monoclonal antibodies
The availability of monoclonal antibodies, especially of the anti-CD20 antibody rituximab, has notably improved the treatment of B-cell lymphomas in recent years. Monotherapy with rituximab resulted in a response in 20–50% of patients with WM (15–17). Because of the lack of myelosuppression, rituximab is an attractive therapeutic option especially in patients with severe cytopenia.

In patients with a very high IgM level at onset (>50 g/l) or high serum viscosity, caution is advised because occasionally, a temporary increase in the IgM value has been observed after rituximab had been administered, which in individual cases increased the viscosity and thus resulted in further complications (18). Initial observations have shown that rituximab is also efficacious in IgM-associated peripheral neuropathies (19, e2–e5).

Chemotherapy combined with monoclonal antibodies
The most recent treatment strategies have attempted to combine rituximab with cytotoxic drugs. Our own data on the combination of the purine analogue pentostatin with cyclophosphamide and rituximab have shown a favorable profile of side effects, with a lower rate of severe cytopenias, as have often been observed in combination treatment with other purine analogues (20). The multicenter PERLL study, conducted in collaboration with the Deutsche Studiengruppe für niedrig maligne Lymphome (GLSG, the German study group for lymphomas of low malignancy), is planning 6 cycles of rituximab, pentostatin, and cyclophosphamide at 3 week intervals for patients with previously treated and not previously treated WM, followed by 2 years of maintenance therapy with rituximab at 3 month intervals (www.poliklinik-hd.de).

The most persuasive proof so far of the therapeutic use of combining chemotherapy with alkylating agents and rituximab was provided by a prospective, randomized study of primary treatment for WM. The only study up to now, it compared standard CHOP therapy with the combination of rituximab and CHOP in patients with lymphoplasmocytoid or lymphoplasmocytic lymphoma according to the currently valid REAL classification. R-CHOP was found to be significantly superior, with an overall response rate of 94% versus 69% and a mean time to treatment failure of 85 months versus 45 months (21). When treating especially elderly patients according to combined chemotherapy protocols, however, it has to be borne in mind that cytopenias and infections are to be expected and infection prophylaxis may be necessary (22).

High dose treatment with stem cell transplantation
In spite of an initial good response to cytotoxic agents and antibodies, however, all patients will develop a recurrence sooner or later; their disorder will become refractory to treatment after several therapeutic options have been exhausted, and they mostly die from their disease. For this reason, as in other lymphomas of low malignancy, myeloablative therapy with autologous stem cell transplantation (SCT) has been introduced, with a curative intention. In the globally largest series on autologous SCT, which included 14 patients, the median progression free interval was 69 months, with a follow-up observation period of 50 (12 to 121) months (23). The extent to which early autologous SCT really does achieve a prognostic improvement in WM is currently being investigated in a randomized comparison (GLSG, www.lymphome.de).

Only few case reports and small studies have been published regarding allogenic stem cell transplantation (23, e10, e11). Primarily the reduced intensity of the conditioning seems an interesting therapeutic option for young patients with WM, in whom conventional therapies have not resulted in longer term control of the disease.

Treatment strategy
The mainstays of WM therapy are:
- Alkylating cytotoxic agents (chlorambucil)
- Purine analogues (fludarabine, cladribine, pentostatin)
- The monoclonal antibody rituximab.
So far, no sufficient data are available from prospective randomized trials that would justify a general recommendation for one of these therapeutic options. The selection should be made according to individual, patient specific criteria. The substances with the highest likelihood of resulting in remission are the purine analogues. Particularly high remission rates and sometimes even a longer remission period are to be expected mainly by using chemo-immunotherapies including rituximab. Especially in elderly patients, chlorambucil is a good treatment option.

When the disease takes an unfavorable course – in the shape of early recurrence or therapy resistant disease – allogenic stem cell transplantation in the context of prospective studies may be considered if the patient's age and general condition permit this. In a scenario of refractoriness to all 3 treatment groups listed above, therapy with the newer substances may be considered in the context of studies, e.g., thalidomide/dexamethasone, alemtuzumab, bortezomib. A current overview over recent therapeutic options can be found in the summary of the 3rd international workshop on Waldenström's macroglobulinemia (24).

Conclusions
Although WM is a rare disorder, significant progress has been made recently with regard to treatment. Through the targeted and considered use of the substances mentioned, stable control of the disease and a good quality of life can be achieved, often for years. The progress of recent years in the understanding of molecular pathogenesis and pathophysiology help even now in the development of new, targeted drugs and in using these successfully. By supporting the study groups in researching the molecular basis, developing new substances, and conducting large, multicenter studies, it is hoped that in the long term, the life expectancy of patients with WM can be improved.

Conflict of Interest Statement
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REFERENCES
For e-references please refer to the additional references listed below.


ADDITIONAL REFERENCES


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