Rare Manifestations of Multiple Myeloma

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Additional information is available at the end of the chapter

1. Introduction

Multiple myeloma (MM) or plasma cell myeloma, is a haematological disease representing 1-2% of all cancers and about 15% of haematological *malignancies*. The classic form of MM is characterized by generalized neoplastic changes in the bones accompanied by kidney damage, impaired haematopoiesis and susceptibility to infections. In laboratory tests, MM manifests itself by the presence of monoclonal protein, called paraprotein, in serum or urine. This results from the fact that pathological plasma cells produce a complete immunoglobulin (Ig), usually IgG or IgA, or only the kappa or lambda light chains. Solitary myeloma (osseous or extraosseous), non-secretory myeloma and secretory myeloma are rarer forms of MM. Sometimes, however, the clinical picture of MM is quite different from the classic manifestation described in the textbooks. This can cause diagnostic difficulties, thereby delaying treatment.

The atypical clinical and laboratory manifestations and paraneoplastic syndromes concomitant with a diagnosis of MM and described below, as are those that appear in the course of the disease, especially in progression. Although they do not represent a significant percentage of cases, knowledge of the rare clinical and laboratory variants of MM may assist in making a differential diagnosis in cases of doubt.

In addition to their low incidence, rare manifestations of MM share the lack of valid relevant scientific knowledge, which leads to difficulties in making firm therapeutic guidelines. In fact, most of the information on these conditions derives from case reports and/or small series studies, making it rather difficult to develop any uniform treatment approaches. As a result, several of rare manifestations of MM can well be controlled with standard regimens used for classic MM, like for example non-secretory myeloma. However the satisfactory strategies to control some of those conditions, such as plasma cell leukemia, are still unsatisfactory. These issues are best illustrated in the present work in the chapter discussing POEMS syndrome.

Furthermore, rare manifestations of MM are heterogonous also in their underlying cellular and/or molecular mechanisms. These can be either a plasma-cell clone (non-secretory myeloma), paraprotein or cytokines (some of the paraneoplastic disorders). Moreover, paraprotein may exhibit autoantibody activity or aggregate into insoluble depositions. This relates to some other uncommon conditions, including various types of amyloidosis and cryoglobulinemia. In amyloidosis, misfolding of proteins occurs. Otherwise soluble, misfolded protein molecules tend to aggregate as extracellular amyloid fibrils, leading to the damage of the various tissues and organs. In cryoglobulinemia, paraproteins present in circulating blood can become insoluble in a certain temperature, resulting in a wide spectrum of clinical symptoms depending on paraprotein properties (Merlini, Stone 2006).

Below, rare manifestations of MM are described in details. Their relative prevalence/incidence is given in Table 1. Table 2 provides short summary of the diagnostic and clinical characteristics of the rare manifestations of MM, except for POEMS syndrome described in more details in Table 3.

Rare manifestation of MM		Percentage of all MM cases
Non-secretory myeloma		1-5%
Myeloma IgD, IgM and IgE		
	IgD	2%
	IgM	0.2-0.5%
	IgE	Very rare
Plasma cell leukemia		0.5-3.0%
POEMS syndrome		Very rare
Rare paraneoplastic syndromes accompanying myeloma		Extremely rare
Family myeloma		Extremely rare
Supporting references can be found in corresponding sections of the main text.		

Table 1. Rare manifestations of multiple myeloma (MM) and their prevalence/incidence.

Rare manifestation of MM	Major diagnostic criteria
Non-secretory myeloma	Bone marrow cytology and immunohistochemistry: the infiltration of clonal plasma cells. The clinical picture: classic osteolytic lesions and a decrease in the level of normal (non-clonal) immunoglobulins.
Myeloma IgD	Diagnosis: problematic because routine test does not detect the monoclonal protein peak in 60% of patients, and when it is detected, the concentration is usually smaller than 20 g/l. An overproduction of light chains (usually lambda) is observed in 90-96% of patients. The clinical picture: a variant of the light chain disease. Usually affects younger patients, the disease course is more aggressive and often accompanied by amyloidosis and extramedullary infiltrations. Lymphadenopathy, renal failure and hypercalcemia are common. Myopathy and carpal tunnel syndrome can be present.
Myeloma IgM	Diagnosis: the presence of IgM monoclonal protein in serum; it is necessary to differentiate with Waldenström's macroglobulinemia. The clinical picture: the clonal proliferation of plasma cells in bone marrow aspiration and the presence of hypercalcemia, renal failure and osteolytic foci.
Myeloma IgE	Frequent presence of plasma cells in peripheral blood, osteoblastic lesions, hepatosplenomegaly and amyloidosis.
Plasma cell leukemia	Diagnosis: at least 20% plasma cells in a peripheral blood smear and/or the absolute number of plasma cells in the peripheral blood exceeding 2 g/l with a concomitant monoclonal gammopathy. The clinical picture: extraosseous infiltrations, often with the involvement of the central nervous system, and accompanied by organomegaly and lymphadenopathy.
Rare paraneoplastic syndromes accompanying myeloma	Sweet's syndrome: granolocytosis, fever and painful erythematous skin changes caused by skin granulocytic infiltrations that subside following treatment with corticosteroids. Bullous epidermal separation or pemphigus: subepidermal bubbles and secondary ulcers.
Family myeloma	The exact genetic cause remains unknown but autosomal inheritance with low gene penetrance is most probable. An annual immunoelectrophoresis of the urine and serum protein least two cases of MM in first or second-degree relatives are present.

Supporting references can be found in corresponding sections of the main text. Detailed diagnostic criteria of POEMS syndrome can be found in Table 3.

Table 2. Major diagnostic procedures and criteria of rare manifestations of multiple myeloma (MM).

Disease	Definition of the disease	References
POEMS syndrome	All four criteria must be met:	Kyle et al. 2009 Dispenzieri et al. 2003
	1. The presence of the monoclonal protein (in serum and/or in urine), especially the light chain type λ.	Dispenzieri et al. 2007
	2. Peripheral polyneuropathy.	Rajkumar et al. 2011
	3. The presence of at least one "great" criterion:	
	• osteosclerotic changes in the skeletal system	
	• Castleman's disease	
	• high levels of vascular endothelial growth factor.	
	4. The presence of at least one "small" criterion:	
	• the enlargement of the internal organs (liver, spleen, lymph nodes)	
	• pleural effusion, ascites, oedema	
	• abnormal secretion of the endocrine glands (adrenal glands, thyroid, parathyroid, pancreas, gonads, with the exception of diabetes or hypothyroidism)	
	•skin lesions (hyperpigmentation, hypertrichosis, peripheral cyanosis, abnormal structure of the nails)	
	• optic disc oedema,	
	• thrombocythaemia, polycythemia.	

Table 3. The criteria for diagnosis of POEMS syndrome.

2. Non-secretory myeloma

Non-secretory myeloma is one of the least frequent forms of MM. The classic diagnostic methods of immunoelectrophoresis and immunofixation do not detect any monoclonal protein in either urine or serum. These patients are usually referred to a haematologist as part of a diagnosis for anaemia or bone changes. It is estimated that this form represents 1-5% of all MM cases [Kyle et al. 2003, Blade, Kyle 1999]. The diagnosis is based on a bone marrow examination (cytology and immunohistochemistry). This will confirm the infiltration of clonal plasma cells, although immunohistochemical tests do not confirm the existence of light kappa or lambda chains in 15% of patients with non-secretory myeloma. The clinical picture reveals classic osteolytic lesions and a decrease in the level of normal (non-clonal) immunoglobulins [Kyle et al. 2003, Blade, Kyle 1999] in 92% of patients. Although classic diagnostic tests do not indicate the presence of monoclonal protein, the ratio of free light chains in serum (FLCr) is abnormal in more than 2/3 of patients. This test is recommended for these patients to evaluate the effectiveness of the therapy [Durie 2006, Dispenzieri 2009]. A more detailed analysis of the immunofixation test, together with the results of the test for free light chains, allows the presence of monoclonal protein in serum to be ascertained. The proportion of patients with "true" non-secretory myeloma is consequently found to be much smaller than 2%. Repeated bone marrow smear tests are the only way to assess the activity of the disease [Durie 2006] in these patients. Cytogenetic abnormalities in patients with non-

secretory myeloma do not differ from those observed in the secretory form [Blade, Kyle 1999]. Both the prognosis and the therapeutic recommendations are the same for patients with non-secretory myeloma and the classic form of the disease, i.e. secretory myeloma. Some studies, however, indicate that the prognosis for patients with non-secretory myeloma treated using autologous transplantation is better than for the patients suffering from the classic form of the disease [Terpos et al. 2003].

3. Myeloma IgD, IgM and IgE

The monoclonal production of immunoglobulin IgD A is a rare laboratory manifestation of MM, observed in approximately 2% of patients with MM. Diagnostic problems arise from the fact that the routine test does not detect the monoclonal protein peak in 60% of patients, and when it is detected, the concentration is usually smaller than 20 g/l. An overproduction of light chains (usually lambda) is observed in 90-96% of patients. This makes the clinical picture a variant of the light chain disease [Blade, Kyle 1999, Kuliszkiewicz-Janus et al. 2005, Shimamoto, 1991, Blades et al. 1994, Jancelewicz et al. 1975]. The clinical picture is also slightly different, although this usually affects younger patients – the disease course is more aggressive and often accompanied by amyloidosis and extramedullary infiltrations. Lymphadenopathy is observed in 10% of patients [Shimamoto, 1991, Blades et al. 1994]. Renal failure is observed in 33% of cases at the moment of diagnosis and hypercalcemia in 20% [Homan et al. 1990]. The disease is often accompanied by neurological symptoms such as myopathy and carpal tunnel syndrome, which is probably associated with the coexistence of amyloidosis. IgD myeloma is often associated with connective tissue diseases. This can hinder diagnosis due to the resulting low concentration of monoclonal protein. Previous analyses suggest that the mean survival time of patients with IgD MM is 13.7-21 months. This is shorter than for the classic IgG and IgA MM [Blade et al. 1994, Jancelewicz et al. 1975]. More recent analyses, however, indicate that 30% of patients with IgD myeloma live more than 3 years and 20% more than 5 years [Blade et al. 1994]. Shimamoto regards the presence of the lambda chain and leukocytes in excess of 7 g/l as adverse factors responsible for the shorter progression-free time in patients with IgD MM. Depending on the number of prognostic factors, patients are classified into three prognostic groups: 0, 1 and 2 [Shimamoto et al. 1991]. Based on a retrospective analysis of 36 patients undergoing ablative chemotherapy, the probability of 3-year survival and progression-free time were 69% and 38% respectively [Sharma et al. 2010]. Some authors indicate that the use of myeloablative chemotherapy reduces the differences between IgD MM and the classic forms of the disease [Sharma et al. 2010, Maisnar et al. 2008], but this remains a matter for discussion [Morris et al. 2010].

MM IgM is even less frequent (0.2-0.5% of patients with MM) [Reece et al. 2010, MacLennan 1992, Avet-Loiseau et al. 2003]. Although the presence of IgM monoclonal protein in serum is one of the clinical features common to the disease and Waldenström's macroglobulinemia (WM), the overall clinical picture is different. The differing prognoses and therapeutic recommendations make a correct diagnosis all the more important. The clonal proliferation of plasma cells usually observed in bone marrow aspiration, together with other characteristic

clinical features of multiple myeloma such as hypercalcemia, renal failure and osteolytic foci, support a diagnosis of IgM MM much more frequently than a diagnosis of WM. These differential diagnostics may not be easy. Cytogenetic tests are helpful in these situations. Recent study results indicate that the presence of translocation t(11;14) associated with deregulation of cyclin D1 is specific for MM, but not for WM [Avet-Loiseau et al. 2003]. Another differentiating feature is that 6q deletion istypical of WM [Schop et al. 2006]. Some authors, however, indicate the limited sensitivity of cytogenetic testing in diagnosing MM IgM and therefore seek other differential diagnostic tests [Schuster et al. 2010]. One would be an increased expression of interleukin-1b (IL-1b). This substance is responsible for the increased production of interleukin 6 (IL-6) reported in patients with MM [Donovan et al. 2002]. The treatment of patients with IgM MM does not differ substantially from the treatment of patients with the classic form of MM. Some studies however, indicate a significantly worse prognosis compared with the classic forms, i.e. a much shorter survival time and progression-free time in patients with the rare form of MM [Morris et al. 2010]. Mean survival time is 30 months and myeloablative chemotherapy does not alter this prognosis [Reece et al. 2010, Schuster et al. 2010].

IgE myeloma is very rarely detected. Several cases of this variant have been described [Invernizzi et al. 1991, Hagihara et al. 2010, Chiu et al. 2010]. It manifests itself by the frequent presence of plasma cells in peripheral blood, osteoblastic lesions, hepatosplenomegaly and amyloidosis. The clinical course of this form of MM is usually aggressive and patients have a shorter survival time than those with the classic forms (16 months on average). This may be a result of a delayed diagnosis [Macro et al. 1999].

4. Plasma cell leukaemia

Plasma cell leukaemia is one of the most aggressive forms of MM. It is defined according to the Kyle criteria. Diagnosis is predicated on there being at least 20% plasma cells in a peripheral blood smear and/or the absolute number of plasma cells in the peripheral blood exceeding 2 g/l with a concomitant monoclonal gammopathy [Sher et al. 2010, Jimenez-Zepeda]. It should be noted that the presence of plasma cells in peripheral blood is symptomatic of several infectious diseases, e.g. septic shock, parvovirus B19 infection, infectious mononucleosis, and Dengue fever. These diseases, however, are not accompanied by the presence of monoclonal protein and the plasmacytosis abates with the other symptoms [Gawoski, Ooi 2003, Bai et al. 2006].

Plasma cell leukaemia is rare. It is estimated to constitute 0.5-3% of MM [Han et al. 2008]. Two forms of the disease should be distinguished: a primary form identified in the initial diagnosis; and a secondary form symptomatic of pre-existing classic MM. The primary form was more frequent than the secondary in previous analyses, but the number of patients with the primary and secondary forms is now similar [Sher et al.]. Complex cytogenetic abnormalities are found in 70% of cases of plasma cell leukaemia. These usually include hypodiploidia and structural abnormalities of chromosomes 1, 13 and 14 that are similar in both

forms of the disease [Fonseca et al. 2004, Chang et al. 2009, Colovic et al. 2008]. Plasma cell leukaemia is the most aggressive clinical form of MM. Patients usually manifest extraosseous infiltrations, often with the involvement of the central nervous system, and accompanied by *organomegaly* and lymphadenopathy. The aggressiveness of the disease is also demonstrated by the significantly increased activity of serum lactate dehydrogenase, high levels of β2-microglobulin (in 65% of patients > 6 mg/l) and low serum albumin levels.

The prognosis remains poor, especially in the secondary form, where it is a consequence of the progression of the disease and increasing *chemoresistance*. Moreover, resistance very quickly develops in patients with primary leukaemia, despite their initial response to treatment. The average survival time is 8 months for patients with the primary form and 2 months for those with the secondary form [Garcia-Sanz et al. 1999, Tiedemann et al. 2008]. Because of the low incidence of the disease, there are no randomized controlled trials and thus no therapeutic recommendations. Traditional schemes for treatment of MM are usually ineffective. Even though prolongation of survival time was reported in patients after myeloablative chemotherapy assisted by autotransplantation, this treatment was less effective than it was in patients with the classic form of the disease. Allotransplantation is an alternative, especially in the primary disease, which often affects younger people. Due to the limited number of patients and lack of randomized studies, the effects of this treatment are difficult to assess, but previous reports indicate moderate effectiveness and high mortality (the mean survival time is 3 months) [Yeh et al. 1999].

New drugs, such as proteasome inhibitors and immunomodulatory drugs, are promising, although the effectiveness of this treatment remains unsatisfactory. As thalidomide is of limited efficacy and seems to have no significant effect on prolonging survival time in patients with plasma cell leukaemia (reported mean survival time is 3 months) [Petrucci et al. 2007], other authors have been presenting more promising data (survival time up to 14 months) [Johnston, Abdalla 2002]. The use of lenalidomide has enabled a response to be obtained in individual patients, as with resistance to other schemes, but this usually lasts 4-5 months [Musto et al. 2008, Benson and Smith 2007]. The results of bortezomib treatment are slightly more promising. This therapy, especially the combination therapy (VDT-PACE), enables a response to be obtained in more than 90% of patients, including those in whom the disease is initially chemoresistant. Mean survival time is 7-12 months [Albarracin, Fonseca 2011, Musto et al. 2007], although survival times of up to 20 months have also been reported [Sher et al. 2010, Ali et al. 2007]. Bortezomib appears to be able to overcome the adverse effects of cytogenetic abnormalities [Katodritou et al. 2009] – as it does with classic MM – and should therefore be considered a first-line treatment in patients with plasma cell leukaemia.

5. POEMS syndrome

The syndrome was first described in 1956 and was originally named the Crow–Fucasi syndrome. Since 1980, it has been known by the acronym POEMS, derived from the symptoms polyneuropathy, enlarged internal organs (organomegaly), endocrine disorders, monoclonal protein and skin changes.

The pathogenesis of POEMS syndrome is complex and not fully understood. The starting point must be the mutation of the plasma cells producing the light chains (usually λ) as this is what causes its clonal expansion. Karyotype tests of plasma cells usually reveal aneuploidy [Rose et al. 1997] and del13 [Bryce et al. 2007]. Whether a neoplastic clone produces its characteristic symptoms through the direct action of monoclonal protein on some target molecules and the secretion of various cytokines from neoplastic cells, or whether it happens in an indirect manner, is not precisely known. It is believed that high levels of pro-angiogenic and pro-inflammatory cytokines, especially IL-1β, TNF-α, IL-6 and a concentration of vascular endothelial growth factor (VEGF) are essential to the development of the clinical symptoms of POEMS syndrome [Gherardi et al. 1996, Hitoshi et al. 1994].

VEGF is considered to be the most important cytokine responsible for the development of POEMS syndrome. This is the cytokine that reacts with endothelial cells and causes the rapid and reversible increase in vascular filtration essential to angiogenesis and osteogenesis [Endo et al. 2002, Soubrier et al. 1997]. The increased production of VEGF is also a result of high concentrations of IL-1 and IL-6 [Soubrier et al. 1997]. VEGF 165 isoform is most commonly diagnosed. The concentration of VEGF correlates with the progression of the disease, but does not depend on the concentration of monoclonal protein [Watanabe et al. 1998].

POEMS syndrome is very rare. The incidence in Japan is 3 cases per million people per year [Arimura et al. 2007], and this is estimated to be even less in Western Europe and the United States of America. The peak incidence of POEMS syndrome occurs during the fifth and the sixth decades of life [Dispenzieri et al. 2007]. POEMS syndrome is a chronic disease and some patients live more than 10 years. Dispenzieri et al. have found that the mean survival time of patients with POEMS is 13.8 years [Dispenzieri et al. 2003]. In turn, Gherardi et al. have found that 7 out of 15 patients with POEMS syndrome live 5 years or more, including one case of 25 years [Gherardi et al. 1991].

The criteria for diagnosing POEMS syndrome are summarized in Table 3.

The characteristic symptoms of POEMS syndrome should have a temporal relationship. The most important symptom, i.e. the one that enables POEMS to be differentiated from other plasma cell dyscrasias, is the ascertainment of single or multiple osteosclerotic changes. A conclusive diagnosis of POEMS syndrome is unlikely in the absence of bone changes. Skin changes, most commonly hypertrichosis and hyperpigmentation, may occur in POEMS patients. Enlarged mammary glands and testicular atrophy may occur in men. Peripheral blood count abnormalities, especially thrombocythemia and polyglobulia, are frequently detected by morphological examinations.

The concentrations of serum monoclonal protein and the level of Bence-Jones protein in urine are lower than in patients with MM. Renal failure, high calcium plasma concentration, and pathological bone fractures are rarely observed. The percentage of plasma cells is usually less than 5% in bone marrow examinations. High concentrations of IL-1β, TNF-α, IL-6 and VEGF in serum are typical of POEMS [Soubrier et al. 1997].

Polyneuropathy is the predominant clinical symptom (100% of patients with POEMS syndrome) [Kelly Jr. et al. 1983]. Initially, sensory disturbances occur mainly in the lower limbs.

Gait disorders may appear later. This process is progressive and movement is difficult in 50% of patients. This can eventually cause disability. Bone pain and pathologic fractures are rare. Other symptoms include progressive weight loss and muscle atrophy.

About 1/3 of patients develop ascites and fluid in the pleural cavities [Dispenzieri et al. 2007]. In 50% of patients, the liver, and less frequently the spleen and the lymph nodes, is enlarged. A histopathological examination of the enlarged lymph node often indicates angiofollicular lymph node hyperplasia (Castleman's disease) [Dispenzieri et al. 2003, Nakanishi et al. 1984]. Some patients may develop venous and arterial thrombosis [Kang et al. 2003]. Impaired secretion of endocrine glands, most commonly hypogonadism, hypothyroidism, glucose metabolism and adrenal insufficiency, is diagnosed in about 84% of patients. Most patients have impaired secretion in four or more endocrine glands. This may be accompanied by failure of the gonads, thyroid, pancreas and adrenal glands.

Because the predominant symptom is polyneuropathy, patients with POEMS syndrome are initially referred to neurologists - usually with suspected Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy.

Once the monoclonal protein accompanying the polyneuropathy has been detected, a differential diagnosis should include AL, monoclonal gammopathy and MM.

The concentration of VEGF is one of the most sensitive tests to differentiate POEMS syndrome from the other diseases mentioned above. The plasma of patients with POEMS syndrome has a high VEGF concentration. VEGF concentration in patients with the other diseases mentioned above is low [Gherardi et al. 1996, Watanabe et al. 1998].

The rare incidence of POEMS syndrome and the lack of definitive knowledge as to its causes mean that there are no standards of treatment. For the same reason, there are no randomized clinical trial results to evaluate the effectiveness of any given method of treatment. Methods of treating POEMS syndrome patients have mainly been devised from clinical reports, case reports and retrospective observations (usually at a single centre), and the experience gained from treating other plasma cells *dyscrasias*.

Radiotherapy is the treatment of choice for POEMS syndrome patients with isolated bone lesions. If there are numerous bone changes and these coexist with other symptoms typical of POEMS syndrome, it is recommended that patients be treated similarly to those with MM. In older patients, the treatment is based on alkylating drugs, while the therapy for younger patients includes high-dose chemotherapy-assisted auto-SCT [Dispenzieri et al. 2003].

The final confirmation of the hypothesis that VEGF is the major cytokine responsible for the development of POEMS syndrome, will have a significant impact on changing the way that POEMS patients are treated; the way which will be predominantly focused on VEGF..Neither intravenous immunoglobulins nor plasmapheresis treatments benefit patients with POEMS syndrome [Dispenzieri et al. 2007]. The concomitant treatment with plasmapheresis and corticosteroids was found to be more effective [Ku et al. 1995]. Melphalan is the drug that has been used to treat *dyscrasias* the longest. The results of retrospective studies, in

which melphalan was mainly used in combination with prednisone (the treatment duration was 12-24 months), indicate that a response to the treatment was obtained in 40% of patients [Dispenzieri et al. 2003]. Cyclophosphamide allows for remission of the disease in a limited number of patients. This treatment may be used in young patients who are candidates for auto-SCT.

The results of high-dose chemotherapy-assisted auto-SCT are promising [Sanada et al. 2006], as a response is obtained in over 90% of patients (Table 4). Transplant related mortality is determined to be approximately 7%. This is higher than in MM patients treated with auto-SCT and lower than in AL patients treated with auto-SCT [Gertz et al. 2002]. High dose chemotherapy assisted auto-SCT reduces the symptoms of polyneuropathy. When combined with radiotherapy, this reduction can last months or even years [Ganti et al. 2005]. The clinical response to the treatment correlates more closely to the VEGF concentration than to the monoclonal protein level [Nakano et al. 2001]. A *complete* haematological remission is not required to obtain a clinical improvement. The effectiveness of the most common ways of treating patients with POEMS syndrome is shown in Table 4.

Treatment	Response to the treatment	References
Corticosteroids	≥15%	Dispenzieri et al. 2003
		Nakanishi et al. 1984
		Orefice et al. 1994
Treatment with alkylating drugs	≥40%	Dispenzieri et al. 2003
		Reitan et al. 1980
Radiation therapy	≥50%	Dispenzieri et al. 2003
		Iwashita et al. 1977
		Reitan et al. 1980
Auto-SCT	≥90%	Sanada et al. 2006
		Ganti et al. 2005
		Jaccard et al. 2002

Auto-SCT (*auto-stem cells transplantation*) – autologous transplantation of the stem cells obtained from peripheral blood.

Table 4. The effectiveness of the most commonly used treatments in patients with POEMS syndrome.

Apart from the methods of treating POEMS syndrome mentioned above, there are few reports on the effectiveness of therapy combined with bevacizumab and thalidomide in patients diagnosed with a relapse of POEMS syndrome after auto-SCT. The combination of cyclophosphamide, dexamethasone and bevacizumab is another example of a modern combination therapy, described by Samaras et al., to treat POEMS syndrome relapse after auto-PBSCT [Badros et al. 2005, Straume et al. 2006]. There are also case reports describing the treatment of patients with POEMS syndrome using lenalidomide [Dispenzieri et al. 2007]. Recently, Szturz et al. [2012] reported on the successful application of lenalidomide in Cas-

tleman disease, a condition that can accompany POEMS syndrome. Other drugs used to treat POEMS syndrome patients include interferon α [Coto et al. 1991], tamoxifen, trans retinoic acid, thalidomide, ticlopidine, argatroban and strontium (^{89}Sr) [Dispenzieri et al. 2007]. The effectiveness of these drugs is limited and further clinical trials are required.

Lenalidomide seems to be one of the most promising immunomodulatory drugs to treat POEMS syndrome, but further clinical studies are required [Dispenzieri et al. 2007].

High dose chemotherapy assisted auto-SCT remains the best therapeutic method, although it also has the highest mortality rate.

6. Rare paraneoplastic syndromes accompanying myeloma

Sweet's syndrome is one of the paraneoplastic syndromes that may accompany MM. This is a group of symptoms including granolocytosis, fever and painful erythematous skin changes caused by skin *granulocytic* infiltrations that subside following treatment with corticosteroids [Paydas et al. 1993]. These changes are also found in the mouth, the joints and the internal organs. Sweet's syndrome is extremely rare (0.25% of patients with MM) and is most likely caused by an increased sensitivity to the growth factor. This can be explained by an increased production of interleukin 6 (IL-6) [Bayer-Garner, Cottler-Fox, Smoller 2003].

Bullous epidermal separation (epidermolisis bullosa) may also coexist with MM. This is associated with the production of IgG antibodies against the *non-collagenous* domain of type VII collagen. This leads to the formation of subepidermal bubbles and secondary ulcers [Radfar 2006]. Pemphigus has a similar clinical picture. This is a rare complication observed in MM patients and is usually associated with IgA MM. This disease develops extremely rarely and is sometimes also associated with gammopathy of undetermined significance. It has been suggested that treatment should include bortezomib [Adam et al. 2010]. There are many skin symptoms associated with monoclonal gammopathy: leukocytoclastic vasculitis, pyoderma gangrenosum and Schnitzler syndrome. These, however, are rare and discussing them is beyond the scope of this chapter [Harati et al. 2005].

7. Family myeloma

The cause of MM remains unknown [Lynch et al. 2008, Alexander et al. 2007, Morgan, Davies, Lineta 2002]. It seems that the hereditary cause is negligible, although family cases of this cancer have been observed. It has also been described in connection with gammopathy of undetermined significance [Lynch et al. 2008]. Large population studies also indicate that MM, prostate cancer and malignant melanoma run in families, as do central nervous system neoplasms, although the results of some studies do not confirm this [Eriksson, Hallberg 1992, Camp, Werner, Cannon-Albright, 2008]. The risk of familial MM is small. It is estimated that the probability of first-degree relatives developing MM is 3.2 per 1000 cases and

women are usually affected. Autosomal inheritance with low gene *penetrance* is believed to be responsible for the onset of the disease. The risk of familial gammopathy of undetermined significance is slightly higher, although still small. Had there been at least two cases of MM in first or second-degree relatives, an annual immunoelectrophoresis of the urine and serum protein in people 40 years and over would be recommended. If MM had occurred in anyone under 40 years old, the test would be recommended to relatives 35 years and over [Gerkes et al. 2007].

The described forms of MM are extremely rare. They are an important diagnostic problem because of their atypical clinical manifestation. The course of the disease is usually aggressive and the prognosis is serious. It is therefore essential that it be quickly and accurately diagnosed. The lack of prospective studies of large groups of patients is an additional problem. This makes these atypical clinical forms a therapeutic as well as a diagnostic challenge.

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