Pathogenesis and Treatment of Xanthomatosis associated with Monoclonal Gammopathy

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Abstract

Xanthomas are a common manifestation of lipid metabolism disorders. They include hyperlipemic xanthoma (HX), normolipemic xanthoma (NX) and a related condition, necrobiotic xanthogranuloma (NXG). All three forms can be associated with monoclonal immunoglobulin (MIg). In an attempt to improve diagnosis, understanding and treatment of this association, we retrospectively analyzed a personal series of 24 patients (2 HX, 11 NX and 11 NXG) and 230 well-documented reports from the literature.

With the exception of the nodules and plaques featured in NXG, the clinical presentation of xanthomatous lesions usually resembled that seen in common hyperlipidemic forms and could not be used to suspect MIg associated xanthomas. Extracutaneous sites were not rare. The MIg was an IgG in 80% of cases. Associated hematological diseases were monoclonal gammopathy of undetermined significance and multiple myeloma (44% and 35% of cases, respectively).

Hypocomplementemia with low C4 fraction was present in 80% of studied patients. Low C1inhibitor serum levels were found in 53%. Cryoglobulinemia was detected in 27.5%. These abnormalities suggest immune complex formation due to interactions between the MIg and lipoproteins and argue in favor of a causal link between MIg and xanthomas. Monoclonal gammopathy therapy could thus be an option. Indeed, among the patients who received chemotherapy, hematological remission was accompanied by improvement in xanthoma lesions in several cases.
Xanthomas are a common manifestation of lipid metabolism disorders which are characterized by the deposition of yellowish cholesterol-rich material in large foam cells accumulating in the skin and the tendons. Xanthomatosis is usually associated with hyperlipidemias, both primary and secondary types, and morbidity and mortality of this condition are related to atherosclerosis and pancreatitis. Xanthomas can also occur in normolipemic patients although rarely, with the exception of lipid deposits limited to the palpebral area – the so-called xanthelasma (1).

Xanthoma lesions have been described with or without hyperlipidemia in association with monoclonal immunoglobulin (MIg). Cremer et al (2) first reported on this association in 1937. Since then three distinct forms have been identified: hyperlipemic xanthoma (HX), diffuse plane normolipemic xanthoma (NX) and the so-called necrobiotic xanthogranuloma (NXG). Xanthoma lesions in HX and NX are similar (yellow maculae or papules) though NX lesions are usually diffuse and plane whereas HX lesions are more polymorphic and can include tuberous, tendinous, palmar or eruptive xanthoma (3). In contrast, NXG lesions are firm papules, nodules or plaques, the color of which varies from violaceous to red-orange or yellow (4). HX and NX are characterized by foam cell infiltration in the skin whereas NXG is featured by the association of necrobiosis, giant cells (Touton type), asteroid bodies, cholesterol clefts, and foam cells (5).

It could be argued that the association of xanthomatosis with monoclonal gammopathy is fortuitous particularly in the elderly because of the relatively high prevalence of monoclonal gammopathy in this population. However, the anti-lipoprotein activity of MIg has been documented in some patients with HX and NX and this points towards a cause and effect link between the two disorders (3, 6, 7). The physiopathology of NXG remains much less well understood than the two other forms (8). Therapeutic options for patients with xanthoma lesions and associated MIg, which depend on the demonstration of a relationship between
the two disorders, are currently poorly defined. With a view to gaining further knowledge of
the association of xanthoma and MIg, we analyzed a personal series of all patients with
respect to clinical, biological, pathological and therapeutic parameters and compared our
findings with existing data from the literature.

**Patients and methods:**

Ten French medical units of dermatology, internal medicine or hematology were questioned
about any patients with HX, NX or NXG followed between 1980 and 2010. Inclusion criteria
were i) presence of an MIg as detected by serum or urine electrophoresis and/or
immunoelectrophoresis, ii) xanthomatous cutaneous lesions confirmed by a biopsy showing
either foam cell infiltration or necrobiosis, cholesterol clefts and Touton giant cells for
xanthoma and NXG, respectively iii) available tests for plasma cholesterol and triglycerides.
Diagnosis of associated monoclonal gammopathy was established according to the
International Myeloma Working Group. A histopathological examination was usually
required to confirm potential extracutaneous lesions. When this was possible, biopsies of
patient’s skin lesions were stained by the CD 163 antibody (Novocastra Laboratories Ltd
Newcastle UK) and studied by immunohistochemistry. Diagnosis of atherosclerosis was
considered if patient had cardiovascular event in their background or during the follow-up and
taking into account arterial Doppler evaluation when available. In parallel, a Pubmed/Medline
review of the literature was performed using the following key words: “xanthoma
paraprotein”, “diffuse plane normolipemic xanthoma”, “hyperlipidemia myeloma” and
“necrobiotic xanthogranuloma”.
Results

Personal series (Tables 1, 2, 3 & 4)

Data from 24 patients, of whom 17 patients were still alive and seven were lost to follow-up or had died, were retrospectively studied. There were 13 men and 11 women (sex ratio = 1.2). Mean age at diagnosis was 61.25± 11.4 years (range 37 to 78). In 87.5% (21/24) of cases, the skin lesions led the discovery of the Mlg. The periorbital area was involved in 83.5% (20/24) of cases (Table 1, 2 and 3). The skin lesions of cases of NXG were always nodules or plaques (figure 1) whereas those of HX or NX were maculae or papules. One patient with NX had a diffuse xanthodermia (figure 1). Three patients had both NX and NXG (confirmed by pathology). Atherosclerosis was found in 5 patients (21%). Extra-cutaneous lesions were found in 33% (8/24) of cases, mostly in patients with NXG (54.5%). In four patients, this consisted of a symptomatic orbital mass. In the remaining four patients, infiltration by foam cells was discovered on a systematic bone marrow examination (n=3), on the biopsy of an enlarged inguinal lymph node (n=1) and on a hepatic biopsy performed because of abnormalities in liver enzymes (n=1). The Mlg was an IgG in all 24 cases (100%), Kappa (κ) in 15 (62.5%) and Lambda (λ) in nine (37.5%). Three patients had a biclonal gammopathy (two had an IgG and an IgM and one had two IgG). The IgG subclass was IgG1 in the seven cases studied. Underlying monoclonal gammopathy of undetermined significance (MGUS) and Multiple Myeloma (MM) were diagnosed in 14 (58%) and eight (33%) cases, respectively. In addition, Waldenström disease with amyloidosis and B-cell non-Hodgkin lymphoma of lymphoplasmocytic type were diagnosed in one case each. Three patients (patient 3, 7 and 14) (17%) developed myelodysplasia, 2 after being treated by chemotherapy and one at diagnosis. The complement study (table 2) revealed a decrease in CH50 in 83% (16/20) of studied patients, with a low C4 fraction in 95.5% (21/22). The serum C4 level was markedly low (<25% of normal value) in 81% (17/21) of the patients. Unexpectedly, a
decrease in the C1 inhibitor (C1Inh) level was found in 40% (4/10) of cases. A small amount of cryoglobulin was detected in 2/15 patients (13%), of type I and III in one case each. High levels of triglycerides as well as total cholesterol characterized dyslipidemia in HX. In all NXG cases, plasma lipid levels were normal or low.

In all patients, histological findings were in accordance with the selection criteria. In 10 skin biopsy samples, an immunohistochemical study using CD163 staining as a monocyte/macrophage marker was performed. Foam cells as well as Touton giant cells were consistently CD163 positive in all cases of HX, NX and of NXG (figure 2).

Eleven patients were treated by standard-dose conventional chemotherapy and two patients received a high dose regimen (melphalan 200 mg/m2) supported by autologous blood stem cell transplantation (table 1). Skin lesions improved after treatment in eight patients who presented with HX or NXG, whatever the drug (Chlorambucil, melphalan, thalidomide or bortezomib). In these cases, regression of skin lesions was associated with a reduction in the M1g serum level. Of note, the three patients (patient 6, 7 and 22) who achieved an apparent complete hematological response (CR) also experienced a complete dermatological response. When the relapse occurred, it was associated with the reappearance of the skin xanthomatous lesions in these 3 cases. Importantly, in additional patient (case 23) who achieved a sustained hematological and dermatological CR (figure 1) complement serum levels also return to normal values. In the three patients with NX, treatment was unsuccessful on skin lesions and no decrease in M1g level was observed, even in patient 11 who received high-dose melphalan and an autotransplant. In the two HX cases, chemotherapy led to normalization of blood lipid levels.
Comparison with existing literature (Tables 3 & 4)

We reviewed 216 well-described cases of xanthomatosis associated with MIg in the literature, including 37 cases of HX (3), 63 of NX (6, 9-30) and 116 of NXG (4, 8, 31-47) (table 3 and 4). The main patient characteristics are listed in Tables 3 and 4.

The 37 cases of HX included 17 men and 19 women (sex ratio 0.9) with a mean age of 53.9 ± 10.75 years (range 31 to 80). All types of xanthomas were described (plane, eruptive, diffuse, papular). Periorbital involvement was present in 24.3% (9/37) of the patients. Extracutaneous lesions were reported in eight cases (21%) including bone (n=1 (48)), lung (n=1 (49)), hepatic (n=1 (50)), palatine (n=1 (51)) and tendinous (n=4 (52-55)) localizations. Two patients had splenomegaly and one patient had hepatomegaly, without mention of the cause. Cardiovascular disease or atherosclerosis was present in 14 cases (37%). Skin lesions preceded the discovery of the MIg in 92% (34/37) of the cases. The MIg was IgG, IgA and IgM in 38% (n=14), 35% (n=13) and 2.5% (n=1) of patients, respectively. MIg isotype was not reported for nine patients. The underlying hemopathy was MM in 31 (84%), MGUS in four (11%), and chronic lymphocyte leukemia (CLL) and Waldenström’s disease in one case each. Serum complement levels were assessed in only two patients and a low C4 value was reported in one (56). Cryoglobulinemia was found in five of the eight patients studied, without characterization in any of the cases. Type 3 dyslipidemia was the most frequent (63%, 24/38) but all types were reported. Histopathological analysis revealed foam cells in all of the cases with no IgG on immunofluorescence in two. Touton cells were found in two patients. Out of the 15 treated patients (3) treatment was reported as effective in 53% (8/15) of the patients who received standard dose chemotherapy using alkylating agents and steroids (n=6) or Adriamycine and steroids (n=1). In addition, one patient was treated by high dose
therapy and autotransplant which produced both hematological and cutaneous complete remission; at myeloma (and hyperlipemia) relapse, he received an allogeneic transplant but there is no information about subsequent progression of the xanthomatous lesions (3).

The 63 reviewed cases of NX included 32 men and 31 women (sex ratio=1) with a mean age of 62.05 ± 8.76 years (range 37 to 83). Most often, xanthomas were featured by diffuse plane eruptions, but also by maculae, papules, or nodular lesions. Periorbital involvement was present in 51% (32/63). Extra-cutaneous lesions were noted in 12.7% (n=8) including two patients who had several localizations. The most frequent was in the oral cavity (n=5) (16, 57-59). Others included ophthalmic (n=2) (57, 60), digestive (n=1) (61), tendinous (n=1) and muscular (n=1) (16) localizations. In one patient, the aortic valve had been replaced because of severe aortic insufficiency and its histology revealed the presence of foam and Touton cells (57). Atherosclerosis was reported in only one patient (62). In 95% (60/63) of the cases the skin lesions led the clinician to investigate for MIg. The MIg was an IgG in 89% (56/63), K in 55% (28/51) and λ in 45% (23/51). In the 10 studied cases, the IgG belonged to the IgG1 subclass. The underlying hematological condition was MM in 48% (n=30), MGUS in 41% (n=26), myelomonocytic leukemia (n=2), non-Hodgkin lymphoma (n=1) and CLL (n=1). In two cases, amyloid deposits, presumed to be AL, were detected. Hypocomplementemia was found in 84% (26/31) of studied cases. C4 serum values were low in all cases and the C4 serum level was below 25% of the lower limit of the normal value in 15 patients. C1inh level was low in 57% (12/21). Cryoglobulinemia was detected in 16% of the patients (5/31). Pathological analysis revealed foam cells without any Ig deposits on immunofluorescence in the 11 studied cases. Touton cells were found in 10 cases (16%). Seven patients were treated by various standard chemotherapy regimens. Three achieved a partial haematological remission which was accompanied by some improvement in xanthomatous lesions (18, 28,
Of note, one patient received the hypolipemic agent probucol which was reported to be effective on skin lesions (21).

The 130 reviewed cases of NXG included 116 cases associated with an MIg (89%). There were 52 men and 78 women (sex ratio M/F 0.67) with a mean age of 56.2 ± 14.2 years (range 17 to 88). Skin lesions were red-brown nodules or plaques, sometimes with ulcerations or telangiectasia. Periorbital involvement was present in 72%. In 90% of the cases, more than one site was involved. In five patients, xanthoma and NXG were present at the same time (46, 64-67). Extra-cutaneous lesions were reported in 23 cases (17.6%) including six patients with several localizations. They were pulmonary (n=7)(8), cardiac (n=6)(8, 37), in the oral cavity (n=4)(38, 65), orbital (n=3)(8), hepatic (n=2)(8, 37), in the spleen (n=2)(8), medullar (n=1)(68), genital (penis) (n=1)(34), in the mastoid (n=1)(32), facial nerve (n=1)(32), and renal (n=1)(69). In addition, splenomegaly was noted in 22 patients (17%) and hepatomegaly in 17 (13%), without any further information. Ophthalmic manifestations, mainly scleritis, chorioiditis or conjunctivitis, were reported in 29 cases (70). Atherosclerosis was present in 14 (11%). The discovery of the MIg preceded the skin lesions in only two cases (45, 71). The MIg was an IgG in 105 patients (82%), an IgA in four and an IgM in two. MIg isotype was not reported in eight patients. The light chain isotype was K for 71% and λ for 28% of cases. Three patients had a biclonal gammopathy. Hematological diseases were MGUS in 59% (n=68) and MM in 17% (n=20) of cases. Two cases of CLL and four cases of B-cell lymphoma were also reported. One case was also associated with amyloidosis (72). Serum C4 level was low in 70% (23/33) of studied cases, including in six patients in whom it was below 25% of normal value. C1inh level was decreased in 4/6 observations. A serum cryoglobulin was detected in 38.5% (10/26) of studied cases; it was never characterized. Abnormal lipid results were reported in 16% (n=21) of patients. Peripheral leucopenia was present in 43
patients (33%). Pathology study revealed foam cells, necrobiosis (except in 1), and Touton cells in all cases sometimes with cholesterol clefts or asteroid bodies. Immunohistochemistry for CD1a and PS100 (when tested) was always negative. Treatment, which was reported in 71 cases, was successful in 55 (77%) patients who received, melphalan and steroids (n=17), Chlorambucil® (n=16), high dose therapy and auto-transplant (n=1), systemic steroids (n=6), thalidomide (n=3) (32, 73, 74), lenalidomide (n=1) (47), plasmapheresis and hydroxychloroquine (n=1), cyclophosphamide and steroids (n=2), azathioprine (n=2), infliximab (n=1) and local therapy including local steroids injection, surgery, or laser CO2 (n=5). Of note, the xanthomatous lesions of the four patients who received an immunomodulatory drug, usually in combination with dexamethasone, were considered to be improved in all cases. Variations in the MIg level were rarely reported and inconsistent: some reported a decrease in levels accompanied by an improvement in cutaneous lesions (34, 75), while others reported that skin lesions persisted despite a reduction in MIg levels (76).

**Discussion:**

We retrospectively analyzed data from 240 patients presenting with xanthomatosis associated with MIg, including a personal series of 24 patients and 216 case reports that were published in the literature. In nearly all cases (97%), the MIg was discovered subsequent to the skin lesions. Prevalence is slightly higher in women than men and onset is usually in the sixth decade of life (mean age 59.76 years). Xanthomas were localized in the periorbital area in 61% of the cases and on the extremities or members in half. Clinical presentation of xanthomas resembles that seen in general hyperlipidemic forms and is usually not suggestive of the presence of an associated MIg, except for the nodules and plaques, sometimes with an inflammatory aspect, that are characteristic features of the so-called necrobiotic xanthogranuloma (NXG): MIg is found in about 80% of patients with this presentation (8).
Although we lack sufficient data to precisely assess the frequency of xanthomatosis and MIg association, it would seem reasonable to recommend performing at least a serum electrophoresis when faced with a xanthoma lesion, with the exception of isolated xanthelasma, particularly in the absence of abnormalities of serum lipid tests. Indeed, while NX is usually much less frequent than HX, it was reported more often in association with MIg, both in our series and in the literature.

When MIg is present in the setting of xanthoma, it is an IgG in 83% (200/240) of cases and the underlying hematological condition is either MGUS or overt lymphoid malignancies such as myeloma – approximately half of each.

In our experience, a good way of testing whether the association between xanthomatosis and MIg is fortuitous in view of the high prevalence of monoclonal gammopathy in the general population, is to check the serum complement level. Overt complement abnormalities are highly uncommon in patients with xanthoma alone and in patients with a non cryoprecipitating MIg (77), whereas a low serum C4 level was present in all of our patients except one. Data from the literature confirmed that low serum C4 is frequent in such patients as it was detected in about 75% (50/66) of studied cases. In our series, we found that CH50 activity was usually decreased whereas the serum level of the C3 fraction of the complement was variable. A decrease in the level of C1Inh was also frequently observed, both in our series and in the literature. Patients with low C1inh had no symptoms of angioneurotic oedema and, in the two studied cases, no C1Inh antibodies were detected. Of note, a high rate of cryoglobulinemia was found (27.5% of all patients) which may explain complement abnormalities at least in some patients. However, decreases in C4 and C1inh levels were also observed in the absence of detectable serum cryoglobulin. In any case, the complement abnormalities are consistent with an activation of the classical complement pathway which is likely to indicate immune complex formation that may be due to antigen-
antibody interactions between the MIg and various lipoproteins (see below).

Accordingly, this argues in favor of a causal link between the monoclonal gammopathy and the xanthoma lesions. This is reinforced by the normalization of complement values that we observed in one patient who achieved a hematological (and dermatological) CR. Whether or not those patients without detectable complement abnormalities reflect a fortuitous association remains an opened question.

We observed complement abnormalities in all three types of xanthoma associated with Mig, HX, NX and NXG. Additional data suggest that these three conditions may be part of a common syndrome. First, HX and NX lesions can coexist with lesions of NXG in the same patient as seen both in patients from our series and from the literature (46, 64-67). Secondly, the three forms share common histological features, namely the presence of foam cells and of Touton cells. The latter is typically considered as characteristic of NXG and, indeed, we did not find such cells in any of our patients with HX and NX. However, Touton cells have been observed in HX and NX in several cases in the literature (20, 49, 57, 62, 78-85). Moreover, as demonstrated here, foam cells and Touton cells share phenotypic characteristics, including the surface expression of the CD163 antigen, which would suggest a common macrophagic origin. Finally, immune complex formation due to antibody activity of the MIg directed against various lipoproteins appears to represent a common physiopathological pathway leading to a lipid accumulation in the macrophagic cells. In HX and NX, an interaction between the MIg and lipoprotein has been more or less well documented in 16 and 9 cases, respectively (3, 21). In HX, this interaction may alter the lipoprotein linkage to its receptor leading to hyperlipidemia (55), whereas in NX the interaction seems to result in enhanced lipid accumulation in the macrophages (6). Few data are available for NXG but an interaction between the MIg and a lipoprotein and activation of circulating monocytes have been described in one case each (8,9). Assuming a common physiopathology of the three forms of
xanthoma with MIg, the different clinical presentation might be explained by different target
of the MIg, or by host-dependant variable responses to the lipoprotein deposits in monocytes
and macrophages.

Importantly, the incidence of atherosclerosis appears to be low in NX and NXG
whereas it is high in HX. Accordingly, an arterial evaluation should be systematically
performed only in those patients with hyperlipemia. Extension of xanthomatous lesions,
particually outside the skin territory, appears to be more frequent in NXG in which extra
cutaneous lesions were found in 20,5% of evaluable cases. In any case, searching for such
deposits by CT-scan or other imaging techniques should be recommended in patients with
suggestive symptoms.

If we consider then that there is a causal link between the MIg and the xanthoma
lesions, monoclonal gammopathy therapeutic options should be discussed. Indeed,
hematological remission may produce an improvement of xanthoma lesions, as illustrated by
several cases both from our series and from the literature. Moreover, in some of these cases,
myeloma relapse was simultaneously featured by xanthoma relapse. The deleterious effect of
MIg may be modulated by intravenous immunoglobulins though these have been used in only
very few patients, with striking efficacy in two patients with NXG (86). However, most
available therapeutic options aim to reduce MIg production using chemotherapeutic drugs,
either alkylating agents, other classical drugs or the so-called new anti-myeloma agents,
including bortezomib, thalidomide and lenalidomide. These drugs, either incorporated in
standard dose regimen or in high dose protocol with autologous transplantation, are obviously
indicated in patients with xanthoma and overt MM. In contrast, in patients with stage I MM or
even more with MGUS, they should be proposed only in patients in whom the cause and
effect link between the two disorders is documented, i.e., in patients with
hypocomplementemia. In addition, MGUS patients who are candidates for chemotherapy
should present with disabling or “painful” lesions, extracutaneous localization and/or symptomatic atherosclerosis. Patients with NX are usually asymptomatic and, as documented here, currently available chemotherapeutic options appear to be poorly effective in this setting. Accordingly, in the absence of progression of the underlying monoclonal gammopathy, chemotherapy should be proposed only in some patients with NXG and HX. While thalidomide or lenalidomide in combination with dexamethasone may represent a good option, current data are not sufficient to draw any definitive conclusions.

Xanthomas should lead clinicians to search for the presence of a M Ig, especially in patients with NXG or normal blood lipid levels. A good way of testing whether the association is fortuitous or not, is to check serum complement levels. If there is no progression of the underlying monoclonal gammopathy, some patients with hypocomplementemia, mainly those with NXG and HX and with disabling lesions, extracutaneous localization and/or symptomatic atherosclerosis could benefit from chemotherapy.

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Contribution:

Raphael Szalat and Bertrand Arnulf contributed equally to this work.

Raphael Szalat, Bertrand Arnulf and Jean-Paul Fermand designed and performed the research, analyzed data and wrote the paper.

Lionel Karlin, Michel Rybojad, Bouchra Asli, Marion Malphettes, Lionel Galicier, Stéphanie Harel, Florence Cordoliani, Jean Gabriel Fuzibet, Eric Oksenhenler, Jean-Pierre Clauvel and Jean-Claude Brouet recruited patients, analyzed data and reviewed the manuscript.

Marie-Dominique Vignon-Pennamen performed histo-pathological studies, analyzed data and reviewed the manuscript.
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Figure 1: (A and B) NXG in patient 1; (C) NX in patient 12; (D) diffuse xanthodermia featuring NX in patient 11; (E and F) HX in patient 23 before (E) and after chemotherapy (F)
Figure 2: Touton giant cell in a skin biopsy (A) with positive staining for CD163 in immunohistochemistry in NXG (B); Dermal infiltration by spumous cells (C) positive staining for CD163 in NX (D).
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<th>Dg</th>
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<td>Patient 14</td>
<td>NXG</td>
<td>70</td>
<td>M</td>
<td>IgGκκ1</td>
<td>Overt MM</td>
<td>No</td>
<td>Melphalan/Prednisone Interferon Alpha</td>
</tr>
<tr>
<td>Patient 15</td>
<td>NXG</td>
<td>60</td>
<td>M</td>
<td>IgGκκ1</td>
<td>MGUS</td>
<td>No</td>
<td>Chlorambucil</td>
</tr>
<tr>
<td>Patient 16</td>
<td>NXG</td>
<td>68</td>
<td>M</td>
<td>IgGκκ1</td>
<td>MGUS</td>
<td>Yes ischemic cardiopathy, severe arteritis</td>
<td>None</td>
</tr>
<tr>
<td>Patient 17</td>
<td>NXG</td>
<td>66</td>
<td>M</td>
<td>IgGκκ1</td>
<td>MGUS</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Patient 18</td>
<td>NXG</td>
<td>52</td>
<td>M</td>
<td>IgGκκ1</td>
<td>MGUS</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Patient 19</td>
<td>NXG</td>
<td>46</td>
<td>M</td>
<td>IgGκκ1</td>
<td>MGUS</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Patient 20</td>
<td>NXG</td>
<td>42</td>
<td>M</td>
<td>IgGκκ1</td>
<td>MGUS</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Patient 21</td>
<td>NXG</td>
<td>63</td>
<td>M</td>
<td>IgGκκ1</td>
<td>MGUS</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Patient 22</td>
<td>NXG</td>
<td>65</td>
<td>M</td>
<td>IgGκκ1</td>
<td>MGUS</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Patient 23</td>
<td>HX</td>
<td>70</td>
<td>F</td>
<td>IgGκκ1</td>
<td>Overt MM</td>
<td>Yes ischemic cardiopathy,</td>
<td>Bortezomib/Thalidomide/Dexamethasone</td>
</tr>
<tr>
<td>Patient 24</td>
<td>HX</td>
<td>55</td>
<td>M</td>
<td>IgGκκ1</td>
<td>Overt MM</td>
<td>Yes ischemic cardiopathy,</td>
<td>Thalidomide/High dose therapy and autotransplant</td>
</tr>
</tbody>
</table>

Table 1: Characteristics and treatment of patients included in present series (Dg=diagnosis, MIg=monoclonal immunoglobulin; MM=Multiple myeloma, MGUS=monoclonal gammopathy of undetermined significance, PR=partial response, VGPR=very good partial response)

* arterial doppler evaluation
° Chlorambucil, rituximab and even fludarabine in patients 4, 5 and 7 were used more for their immuno-suppressive properties rather than as anti-proliferative drugs.
<table>
<thead>
<tr>
<th>Patients</th>
<th>CH50</th>
<th>C3</th>
<th>C4</th>
<th>Cryoglobulin</th>
<th>C1inh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt 1</td>
<td>0%</td>
<td>Low</td>
<td>&lt;15%</td>
<td>Negative</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Pt 2</td>
<td>66%</td>
<td>Normal (0.87 mg/L)</td>
<td>&lt;25%</td>
<td>Negative</td>
<td>NA</td>
</tr>
<tr>
<td>Pt 3</td>
<td>75%</td>
<td>Normal (1.3 mg/L)</td>
<td>&lt;25%</td>
<td>Negative</td>
<td>Normal</td>
</tr>
<tr>
<td>Pt 4</td>
<td>Low*</td>
<td>Normal</td>
<td>40%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pt 5</td>
<td>Low*</td>
<td>Low*</td>
<td>Low*</td>
<td>Negative</td>
<td>NA</td>
</tr>
<tr>
<td>Pt 6</td>
<td>NA</td>
<td>Normal</td>
<td>Very low*</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pt 7</td>
<td>NA</td>
<td>Normal</td>
<td>&lt;25%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pt 8</td>
<td>NA</td>
<td>&lt;40%</td>
<td>Negative</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pt 9</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pt 10</td>
<td>&lt;10%</td>
<td>&lt;50%</td>
<td>&lt;5%</td>
<td>NA</td>
<td>Low (0.19g/l)</td>
</tr>
<tr>
<td>Pt 11</td>
<td>Normal</td>
<td>Normal</td>
<td>&lt;25%</td>
<td>NA</td>
<td>Normal</td>
</tr>
<tr>
<td>Pt 12</td>
<td>Low*</td>
<td>Normal</td>
<td>Very low*</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pt 13</td>
<td>25%</td>
<td>Normal (1.04 mg/L)</td>
<td>&lt;25%</td>
<td>Negative</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Pt 14</td>
<td>&lt;25%</td>
<td>75%</td>
<td>&lt;25%</td>
<td>Negative</td>
<td>&lt;30%</td>
</tr>
<tr>
<td>Pt 15</td>
<td>Normal (83%)</td>
<td>Normal</td>
<td>Normal (0.9 mg/L)</td>
<td>Normal</td>
<td>3)</td>
</tr>
<tr>
<td>Pt 16</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
<td>Negative</td>
<td>NA</td>
</tr>
<tr>
<td>Pt 17</td>
<td>Low*</td>
<td>Normal (1.02 mg/L)</td>
<td>&lt;10%</td>
<td>Negative</td>
<td>Normal</td>
</tr>
<tr>
<td>Pt 18</td>
<td>Normal</td>
<td>Normal</td>
<td>&lt;10%</td>
<td>NA</td>
<td>Normal</td>
</tr>
<tr>
<td>Pt 19</td>
<td>&lt;25%</td>
<td>Normal</td>
<td>&lt;10%</td>
<td>Negative</td>
<td>Normal</td>
</tr>
<tr>
<td>Pt 20</td>
<td>15%</td>
<td>Normal</td>
<td>&lt;25%</td>
<td>Negative</td>
<td>NA</td>
</tr>
<tr>
<td>Pt 21</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pt 22</td>
<td>&lt;25%</td>
<td>83%</td>
<td>&lt;25%</td>
<td>Negative</td>
<td>0%</td>
</tr>
<tr>
<td>Pt 23**</td>
<td>&lt;25%</td>
<td>Normal</td>
<td>&lt;25%</td>
<td>Negative</td>
<td>NA</td>
</tr>
<tr>
<td>Pt 24</td>
<td>&lt;25%</td>
<td>45%</td>
<td>&lt;25%</td>
<td>Negative</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 2: Characteristics of complement, C1 inhibitor levels and cryoglobulinemia
(NA: not available; very low: less than 25% of the normal range, Deficiency: less than 30% of the normal range)

* Corresponding value not available  ** Normalization of complement levels while chemo-induced CR (Only one case with available complement values on chemotherapy)
<table>
<thead>
<tr>
<th></th>
<th><strong>HX</strong></th>
<th><strong>NX</strong></th>
<th><strong>NXG</strong></th>
<th><strong>Total</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nb cases</strong></td>
<td>37</td>
<td>2</td>
<td>63</td>
<td>110</td>
</tr>
<tr>
<td><strong>Mean age (range)</strong></td>
<td>53.9 (31 to 80)</td>
<td>62.05 (37 to 83)</td>
<td>56.9 (37 to 75)</td>
<td>56.23 (17 to 88)</td>
</tr>
<tr>
<td><strong>Sex ratio</strong></td>
<td>1.2 (19/17)</td>
<td>1 (31/32)</td>
<td>0.2 (2/9)</td>
<td>1.5 (78/52)</td>
</tr>
<tr>
<td><strong>Extra cutaneous lesions</strong></td>
<td>9/37</td>
<td>0/1</td>
<td>32/63</td>
<td>10/11</td>
</tr>
<tr>
<td><strong>Cryoglobulinemia</strong></td>
<td>5/8</td>
<td>0/2</td>
<td>5/31</td>
<td>2/8</td>
</tr>
<tr>
<td><strong>M1g Isotype</strong></td>
<td>14 IgG</td>
<td>2 IgG</td>
<td>56 IgG (89%)</td>
<td>11 IgG</td>
</tr>
<tr>
<td></td>
<td>13 IgA</td>
<td>13 IgA</td>
<td>1 IgM K, 1 IgM λ, 1 IgA, 1 BJ K, 4 UK</td>
<td>105 IgG (81%)</td>
</tr>
<tr>
<td><strong>Associated gammopathy</strong></td>
<td>31 MM</td>
<td>2 MM</td>
<td>30 MM</td>
<td>2 MM</td>
</tr>
<tr>
<td></td>
<td>4 MGUS</td>
<td>26 MGUS</td>
<td>8 MGUS</td>
<td>20 MM</td>
</tr>
<tr>
<td></td>
<td>1 CLl</td>
<td>2 MMCL, 1 CLl, 1 NHL</td>
<td>1 Waldenström</td>
<td>4 MM</td>
</tr>
<tr>
<td></td>
<td>1 Waldenström</td>
<td>2 CLL, 3 NHL, 1 HL, 22 UK</td>
<td>1 NHL</td>
<td>90 MM (35.4%)</td>
</tr>
<tr>
<td><strong>Low serum C4 fraction level</strong></td>
<td>0/1</td>
<td>2/2</td>
<td>26/31</td>
<td>9/10</td>
</tr>
<tr>
<td><strong>&lt; 25% of normal values</strong></td>
<td>0/1</td>
<td>2/2</td>
<td>15/26</td>
<td>8/9</td>
</tr>
<tr>
<td><strong>Low C1 inhibitor level</strong></td>
<td>0/1</td>
<td>NA</td>
<td>12/21</td>
<td>2/6</td>
</tr>
</tbody>
</table>

Table 3: Literature data (UK= unknown; Bj= bence jones proteinuria; MMCL= myelomonocytic chronic leukemia; CLl= chronic lymphoid leukemia; NHL= non-Hodgkin lymphoma; HL= Hodgkin lymphoma; NXG= necrobiotic xanthogranuloma; NX= normolipemic xanthoma; HX= hyperlipemic xanthoma)

- Corresponding to available values
## Table 4: Xanthoma topography (NXG= necrobiotic xanthogranuloma; NX= normolipemic xanthoma; HX= hyperlipemic xanthoma).

<table>
<thead>
<tr>
<th>Topography</th>
<th>HX</th>
<th>NX</th>
<th>NXG</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Literature n=38</td>
<td>Present series n=2</td>
<td>Literature n=63</td>
<td>Present series n=11</td>
</tr>
<tr>
<td>Periorbital/Xanthelasma</td>
<td>9 (24%)</td>
<td>2 (100%)</td>
<td>32 (51%)</td>
<td>10/11</td>
</tr>
<tr>
<td>Trunk</td>
<td>11 (29%)</td>
<td>1/2</td>
<td>28 (44%)</td>
<td>6/9</td>
</tr>
<tr>
<td>Folds/Hand</td>
<td>17 (45%)</td>
<td>1/2</td>
<td>26 (41%)</td>
<td>7/11</td>
</tr>
<tr>
<td>Members (arms/legs)</td>
<td>25 (66%)</td>
<td>2/2</td>
<td>27 (43%)</td>
<td>10/11</td>
</tr>
<tr>
<td>Face</td>
<td>4 (10.5%)</td>
<td>0/2</td>
<td>7 (11%)</td>
<td>5/11</td>
</tr>
<tr>
<td>Diffuse Xanthoderma</td>
<td>1 (2%)</td>
<td>0/2</td>
<td>8 (13%)</td>
<td>1/11</td>
</tr>
<tr>
<td>Extra cutaneous</td>
<td>1 bone</td>
<td>1/2</td>
<td>1 conjunctivitis</td>
<td>1/11</td>
</tr>
<tr>
<td></td>
<td>1 Hepatic</td>
<td>Medullar</td>
<td>1 episcleritis</td>
<td>lymph node</td>
</tr>
<tr>
<td></td>
<td>1 lung</td>
<td>5 oral cavity</td>
<td>1 digestive</td>
<td>1 muscle</td>
</tr>
<tr>
<td></td>
<td>1 Palatine</td>
<td>1 aortic valve</td>
<td>1 tendinous</td>
<td>3 orbit</td>
</tr>
</tbody>
</table>
Pathogenesis and treatment of xanthomatosis associated with monoclonal gammopathy

Raphael Szalat, Bertrand Arnulf, Lionel Karlin, Michel Rybojad, Bouchra Asli, Marion Malphettes, Lionel Galicier, Marie-Dominique Vignon-Pennamen, Stéphanie Harel, Florence Cordoliani, Jean Gabriel Fuzibet, Eric Oksenhendler, Jean-Pierre Clauvel, Jean-Claude Brouet and Jean-Paul Fermand