OBJECTIVES: To investigate skin manifestations of the polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome and their correlation with serum vascular endothelial growth factor (s-VEGF-A) levels and to describe the impact of autologous peripheral blood stem cell transplantation (aPBSCT) on these manifestations and the correlation with s-VEGF-A levels.

RESULTS: In 21 patients with skin manifestations at POEMS syndrome diagnosis, the most common skin manifestations were hemangiomas (18 patients [86%]), hyperpigmentation (16 [76%]), skin thickening (12 [57%]), acrocyanosis (12 [57%]), hypertrichosis (11 [52%]), acquired facial lipoatrophy (11 [52%]), and white nails (8 [38%]). The median s-VEGF-A level was not different between patients with and without skin manifestations except in those with hypertrichosis ($P = .04$). After aPBSCT, no significant correlation was observed between s-VEGF-A level decreases and response of skin manifestations, again except for hypertrichosis ($P = .007$).

CONCLUSIONS: Acquired facial lipoatrophy and livedo should be added to the skin manifestations of POEMS syndrome. Despite a role of s-VEGF-A in various skin manifestations, the impact of s-VEGF-A level decreases on skin outcomes is weak after aPBSCT, mostly resulting in clinical stabilization.

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THE POEMS SYNDROME, or Crow-Fukase syndrome, is a rare plasma cell disorder characterized by polyneuropathy, organomegaly, endocrinopathy, serum monoclonal M protein, and skin changes. Although the skin changes do not influence the prognosis, their recognition is useful for establishing the diagnosis. Most skin manifestations are reported in neurologic or hematologic series, which causes a bias in report of the prevalence of these manifestations. Many reports highlight the key role played by elevated levels of serum vascular endothelial growth factor (s-VEGF-A) in this syndrome, presumably secreted by clonal plasma cells. No data are available correlating POEMS syndrome skin manifestations with s-VEGF-A serum levels, but there are studies describing the critical role played by VEGF in various skin signs in patients without POEMS. The objectives of this dermatologic study were to investigate skin manifestations of POEMS syndrome and their correlation with s-VEGF-A levels and then to describe the impact of autologous peripheral blood stem cell transplantation (aPBSCT) on these skin manifestations and s-VEGF-A levels.

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respectively on patients’ photographs at the time of and before diagnosis.

Tuberous hemangiomas were defined as firm, red to violaceous, dome-shaped papules or nodules measuring 0.5 to 1.0 cm, well circumscribed, with a warty appearance and a large base or pedicle. Cherrylike hemangiomas were indistinguishable from senile hemangiomas found in the older healthy population. Edema was not recorded as a skin manifestation.

All patients were studied for endocrinologic disturbances, M-components, and cryoglobulinemia. Skin biopsies were performed in cases of hemangiomas, skin thickening, and infiltrated livedo with necrosis.

### TREATMENTS AND RESPONSE

Ten patients were treated with melphalan hydrochloride, 200 mg/m², followed by aPBSCT. Median time from diagnosis of POEMS syndrome to aPBSCT was 4.5 months (range, 2.3-21.4 months). No major morbidity was observed during the course of the transplantation regimen. One patient (patient 9) was treated with bevacizumab 12 months after aPBSCT because of neurologic progression.

The 10 patients treated by aPBSCT were prospectively observed and carefully evaluated for skin changes at various times (every 3 to 6 months), with a mean follow-up of 34 months (range, 14-87 months). Skin changes were separately scored as response if the skin manifestation disappeared or at least decreased by more than 50% for at least 3 months, progression if the skin manifestations worsened, and skin stabilization if the change in the appearance fulfilled neither response nor progression criteria. A global skin evaluation after aPBSCT was used to quantify changes. An overall skin response was defined as a response in all skin manifestations, and overall skin stabilization was defined as at least stabilization among all skin manifestations.

The clinical neurologic assessment and the electrophysiologic study have been previously described. Patients were considered to have responded to treatment if the disability-modified Rankin score improved by 1 point and the summed value of compound muscle action potential amplitudes of the tibial, peroneal, median, and ulnar nerves improved by 2 mV. A patient's condition was considered to have worsened if the disability score progressed by 1 point and the summed value of compound muscle action potential amplitudes had decreased by at least 1 mV. Stabilization was the rating in cases in which there was no significant change in these scores.
QUANTITATIVE DETECTION OF s-VEGF-A

Serum samples from 20 healthy volunteers (10 women and 10 men with an age range of 25-55 years) and from patients with POEMS syndrome were collected at diagnosis in serum separator tubes for serum or EDTA plasma and kept frozen at −80°C until assay.

Similar samples were also collected from patients treated with aPBSCT 2 to 8 months after treatment. Two patients had further determinations of s-VEGF-A levels from 9 to 28 months after aPBSCT. Testing of serum samples was performed with the agreement of a local ethics committee in accordance with the rules of French legislation.

The s-VEGF-A concentrations were measured in the serum by means of a monoclonal antibody–based enzyme-linked immunosorbent assay test (Quantikine Human VEGF; R&D Systems, Minneapolis, Minnesota). The intensity of developed color was measured at 450 nm adjusted to 570 nm by means of a microtiter plate reader (eASYS UVM 340; Biochrom Ltd, Cambridge, England). Each sample was tested in duplicate and the results were expressed in picograms per milliliter. Standard curves were constructed by using serial dilutions of recombinant human VEGF antigen. The lower detection limit of this assay was 5 pg/mL, which is the concentration corresponding to a signal 20 SDs above the mean of a zero calibrator.

Table 2. Pretreatment s-VEGF-A Levels According to Skin Changes in Patients With POEMS Syndrome

<table>
<thead>
<tr>
<th>Skin Change</th>
<th>No. (%) of Patients (n=21)</th>
<th>s-VEGF-A, pg/mL, Median (Range)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemangioma</td>
<td>18 (86)</td>
<td>1917.5 (521.8-2256.0)</td>
<td>.08</td>
</tr>
<tr>
<td>No</td>
<td>3 (14)</td>
<td>1473.9 (954.6-2081.3)</td>
<td></td>
</tr>
<tr>
<td>No. of hemangiomas ≤10</td>
<td>13 (72)</td>
<td>1800.0 (521.9-2100.6)</td>
<td>.06</td>
</tr>
<tr>
<td>&gt;10</td>
<td>5 (28)</td>
<td>1994.0 (1449.6-2256.0)</td>
<td></td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>16 (76)</td>
<td>1859.0 (521.9-2256.0)</td>
<td>.47</td>
</tr>
<tr>
<td>No</td>
<td>5 (24)</td>
<td>1948.7 (954.6-1148.1)</td>
<td></td>
</tr>
<tr>
<td>Skin thickening</td>
<td>12 (57)</td>
<td>1967.1 (521.9-2085.0)</td>
<td>.62</td>
</tr>
<tr>
<td>No</td>
<td>9 (43)</td>
<td>1895.0 (929.7-2256.0)</td>
<td></td>
</tr>
<tr>
<td>Raynaud phenomenon and/or acrocyanosis</td>
<td>12 (57)</td>
<td>1868.0 (521.9-2100.6)</td>
<td>.97</td>
</tr>
<tr>
<td>No</td>
<td>9 (43)</td>
<td>1899.3 (675.8-2256.0)</td>
<td></td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>11 (52)</td>
<td>1994.4 (1029.2-2256.0)</td>
<td>.04</td>
</tr>
<tr>
<td>No</td>
<td>10 (48)</td>
<td>1797.7 (521.9-2081.3)</td>
<td></td>
</tr>
<tr>
<td>Facial lipoatrophy</td>
<td>11 (52)</td>
<td>1967.1 (675.8-2256.0)</td>
<td>.38</td>
</tr>
<tr>
<td>No</td>
<td>10 (48)</td>
<td>1847.7 (521.9-2100.6)</td>
<td></td>
</tr>
<tr>
<td>White nails</td>
<td>8 (38)</td>
<td>1981.5 (929.7-2087.3)</td>
<td>.31</td>
</tr>
<tr>
<td>No</td>
<td>13 (62)</td>
<td>1850.0 (521.9-2256.0)</td>
<td></td>
</tr>
<tr>
<td>Infiltrated livedo</td>
<td>6 (29)</td>
<td>1980.0 (575.8-2256.0)</td>
<td>.90</td>
</tr>
<tr>
<td>No</td>
<td>15 (71)</td>
<td>1850.0 (521.8-2031.3)</td>
<td></td>
</tr>
<tr>
<td>Digital clubbing</td>
<td>5 (24)</td>
<td>1850.0 (521.8-2081.0)</td>
<td>.25</td>
</tr>
<tr>
<td>No</td>
<td>16 (76)</td>
<td>1957.9 (675.8-2256.0)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; s-VEGF-A, serum vascular endothelial growth factor.

STATISTICAL METHODS

A nonparametric method, the Mann-Whitney test, was used for statistical comparisons. Correlations between clinical variables and s-VEGF-A level were calculated with the Spearman r test. Two-sided P values less than .05 were considered positive. All computations were done with the SAS statistical package V8.02 (SAS Institute Inc, Cary, North Carolina) using BASE, STAT, and GRAP modules. Two-sided P values less than .05 were considered statistically significant.

RESULTS

Characteristics of the patients with POEMS syndrome are shown in Table 1. No patient had coexistent Castleman disease. The median age was 59 years (range, 33-79 years). Eighteen patients were natives of Europe, 3 were from French overseas territories (2 from Caribbean islands and 1 from Tahiti), 1 was from sub-Saharan Africa, and 1 was from Asia. The median delay between the first clinical manifestations and diagnosis of POEMS syndrome was 16 months (range, 2-101 months). Initial clinical manifestations of POEMS syndrome were polyneuropathy (18 patients [78%]), skin manifestations (2 [9%]), asthenia (2 [9%]), and hypoacusia (1 [4%]).

Twenty-one patients (91%) had skin manifestations, occurring within a median period of 7 months (range, 1-101 months) before diagnosis of POEMS syndrome. The manifestations were the initial symptom in 2 cases: they preceded the diagnosis of POEMS syndrome in one case by 48 months and in the second case by 101 months. Skin manifestations are detailed in Table 2. The most common skin manifestations were hemangiomas (in 18 patients [86%]), either clinically tuberous (10 [56%]) or cherrylike (8 [44%]). They were mainly localized on the trunk (14 [78%]) and extremities (4 [22%]) (Figure 1). Hyperpigmentation (in 16 patients [76%]) was ob-
served on sun-exposed areas (13 patients [81%]), on non-exposed areas (6 [38%]), or on both (4 [25%]) (Figure 2). Skin thickening (in 12 patients [57%]) was present on extremities (8 [67%]) and/or on the trunk (6 [50%]). It was diffuse or circumscribed, with or without erythema. In 1 case, an extensive purple plaque was overlying a solitary plasmacytoma of the iliac crest. Acrocyanosis (in 12 of 21 patients [57%]) was also associated with Raynaud phenomenon (3 [14%]) (Figure 3). Hypertrichosis (11 [52%]) was prominent on the head and limbs, especially on the anterior side of the upper parts of the legs and knees, with coarse long black hairs (Figure 4). Acquired facial lipoatrophy (11 [52%]) was bilateral and symmetric, located on the Bichat fat pad (Figure 5). Other dermatologic lesions consisted of white nails (8 [38%]), infiltrated livedo with necrosis (6 [29%]) (Figure 6) as an initial manifestation localized on the ankles and feet (4 [19%]) or a late manifestation with diffuse lesions mainly localized on the trunk (2 [9%]), and digital clubbing of fingers and toes (5 [24%]).

HISTOPATHOLOGY

Skin biopsies were performed on 17 patients with hemangiomas, 7 patients with skin thickening, and 3 patients with infiltrated livedo with necrosis. Biopsy specimens of hemangiomas showed a specific glomeruloid pattern in only 3 of the 17 samples. This pattern through the dermis consisted of dilated vascular spaces containing a conglomeration of capillaries filled with red blood cells closely resembling renal glomeruli. It was exclusively observed in 3 of the 7 tuberous hemangiomas subjected to biopsy (Figure 7). Among the 8 samples from a skin-thickening manifestation, only 3 showed a slight sclerosis of the dermis with vascular hyperplasia. Thrombosis without vasculitis was present in deep dermal or hypodermal arterioles in 3 biopsy specimens from patients with infiltrated livedo with necrosis and without cryoglobulinemia.

BASELINE s-VEGF-A LEVELS AND RELATIONSHIP WITH CLINICAL VARIABLES

Serum s-VEGF-A levels were detectable in healthy subjects and patients with POEMS syndrome. Levels were significantly higher ($P<.001$) in patients (mean [SD], 1718 [487.8] pg/mL) than in healthy subjects (98.80 [101.3] pg/mL).

The s-VEGF-A levels and the pathological characteristics of the patients are detailed in Table 1. No relationship was observed between s-VEGF-A levels and age, sex, ethnic origin, organomegaly, endocrinopathy, edema, and sclerotic bone lesions. However, the s-VEGF-A level was significantly higher in patients with neuropathy as the initial symptom ($P=.01$) than in those without it.
The relationship between the skin changes observed in 21 patients and serum VEGF levels is given in Table 2. When skin changes were taken into account, the median s-VEGF-A level was higher in patients with skin changes (median, 1868.0 pg/mL; range, 521.9-2256.0 pg/mL) than in those without changes (median, 1451.8 pg/mL; range, 954.6-1948.7 pg/mL), but this difference was not significant ($P = .45$). By contrast, a high median s-VEGF-A level was statistically related to hypertrichosis ($P = .04$). Patients with more than 10 hemangiomas had a higher s-VEGF-A level than did patients without hemangiomas or with 10 or fewer; however, these differences were only marginally significant ($P = .08$ and .06, respectively).

**PATIENT OUTCOMES AFTER TREATMENT**

Six patients had a neurologic response, 3 patients achieved stabilization, and 1 patient had progression of the neurologic disorder. The overall skin score showed a response in 2 of 9 patients (22%) and stabilization in 7 (78%). No progressive skin manifestations were observed during clinical follow-up. The evolution of the different skin manifestations is detailed in Table 3.

**POSTTREATMENT s-VEGF-A LEVELS**

Nine patients had s-VEGF-A levels measured after aPBSCT; 1 patient did not undergo follow-up after aPBSCT. The median time between aPBSCT and s-VEGF-A follow-up was 2 months (range, 2-8 months). The s-VEGF-A levels decreased significantly after aPBSCT ($P = .002$) (Figure 8). The median percentage decrease
in s-VEGF-A levels was 37% (range, 2% to 85%). Taking neurologic responses into consideration, the median percentage rate of decrease in s-VEGF-A levels was higher (82%) in the 5 patients with responses to treatment than in the 4 patients who had stabilization or progression (66%). No significant correlation was observed between decreases in s-VEGF-A levels and overall skin responses except for hypertrichosis ($P = .007$) (Figure 9).

Patients 3 and 9 underwent a long follow-up (Figure 10). Patient 3 had a slight decrease in s-VEGF-A levels with a stable skin response and stable neurologic deficit. Patient 9, treated with bevacizumab therapy 12 months after aPBSCT, had a dramatic decrease in s-VEGF-A levels, from 1655.0 pg/mL (at 9 months) to 687.0 pg/mL (a 2.4-fold decrease) 2 months after the start of the bevacizumab treatment. The s-VEGF-A levels (135-92 pg/mL) were then normalized for the next 16 months, contrasting with stable skin response and progressive neurologic deficit.

**COMMENT**

Skin changes are prevalent in POEMS syndrome.$^{14,16-19}$ However, there are few data in the literature on the dermatologic manifestations in POEMS syndrome and their correlation with s-VEGF levels.

Polyneuropathy constitutes the most frequent POEMS syndrome manifestation in previous studies$^{7,18,20}$ and is more disabling than skin changes, which are less frequently the initial manifestation.$^{21}$ Among them, hemangiomas were especially frequent, observed in 86% of
our case patients with skin manifestations. In other studies the prevalence was lower, ranging from 9% to 44%. This higher prevalence may be explained by the systematic dermatologic examination of all patients of this series independently of their reported symptoms. The high prevalence (52%) of facial acquired lipoatrophy preceding POEMS diagnosis was striking because this manifestation associated with POEMS was previously reported in only a few cases. Similar acquired facial lipoatrophy may develop secondary to highly active antiretroviral therapy in patients with human immunodeficiency virus infection or in patients with lupus panniculitis. In POEMS syndrome, this clinical manifestation was not linked to metabolic abnormalities, such as dyslipidemia (5 of 11 patients had normal lipid levels) or diabetes mellitus (3 of 11 had hyperglycemia). Facial acquired lipoatrophy associated with POEMS syndrome was not preceded by a deep skin infiltration as in lupus panniculitis. In the absence of antiretroviral therapy, acquired facial lipoatrophy not preceded by skin infiltration should be suggestive of POEMS syndrome, especially in patients with polyneuropathy and monoclonal gammopathy. The monoclonal gammopathy component usually consists of IgA heavy chain with a light chain. However, POEMS syndrome occurring with IgM heavy chain or with a light chain have been reported previously. All of the patients in this series fulfilled the criteria of Dispenzieri et al for POEMS syndrome, including those with IgM heavy chain or light chain who had dermatologic and extradermatologic manifestations similar to those of the other patients.

On histopathological examination, the suggestive glomeruloid pattern was exclusively observed in biopsy specimens originating from 30% of tuberous hemangiomas. The cherrylike angiomas showed only vascular thickening, which was clinically evident. Biopsies should therefore be performed only on tuberous hemangiomas. Skin thickening was rarely (37%) associated with dermal fibrosis. Thus, pseudosclerosis may be a more appropriate term than skin thickening for this clinical presentation. Localized dermal fibrosis proximal to a plasmacytoma was, however, present in 1 case patient. This lesion resembled an aspect described as AESOP syndrome (adenopathy and extensive skin patch overlying a plasmacytoma), which has been previously described in 2 patients with POEMS syndrome. The infiltrated livedo was not mentioned in previous series; it may be an early circumscribed manifestation without prognostic significance or a late clinical manifestation, suggestive of an upcoming lethal outcome. The presence of skin vessel thrombosis without vasculitis in 3 infiltrated livedos with necrosis demonstrated that thrombosis occurs not only in arteries and veins but also in microcirculation. Thrombosis was also described in vasa nervorum of involved nerves; thus, a common mechanism may be responsible for both manifestations. Vascular endothelial growth factor is a potent, multifunctional cytokine inducing angiogenesis and microvascular hyperpermeability. It is secreted by plasma cells and platelets, and several studies have highlighted the role of high VEGF levels in POEMS syndrome, with mean values greater than 1500 pg/mL. We confirmed that s-VEGF-A level before treat-
increases after aPBSCT may not be sufficient to inhibit angiogenesis with vessel reduction or clearing. Regression of tuberous hemangiomas has been described only in a patient with POEMS syndrome treated directly with bevacizumab.22

Bevacizumab is a selective humanized monoclonal antibody against VEGF. Its efficacy as an antiangiogenic treatment in POEMS syndrome after aPBSCT treatment has been reported by Badros et al.26 The use of bevacizumab is controversial because some reports have shown a worsening of neurologic deficit and, in some cases, sudden death.57,58 In this study, no neurologic improvement was observed after bevacizumab treatment of 1 case, despite a drastic decrease in the s-VEGF-A level after antiangiogenic therapy and the maintenance of low levels during follow-up. The possible correlation between decrease in s-VEGF-A level induced by antiangiogenic therapy with aPBSCT and clinical response needs to be evaluated in further series.

In conclusion, acquired facial lipoatrophy and livedo should be added to the skin manifestations of POEMS syndrome. Despite a role of s-VEGF-A in various skin manifestations, the impact of decreases in s-VEGF-A level on skin outcomes was weak after aPBSCT, mostly resulting in clinical stabilization.

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Author Contributions: Drs Barete and Mouawad may be considered co-first authors. Drs Barete and Mouawad had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Barete, Mouawad, Khayat, and Francès. Acquisition of data: Barete, Mouawad, Choquet, Viala, Leblond, Musset, Amoura, and Francès. Analysis and interpretation of data: Barete, Mouawad, Choquet, Amoura, and Francès. Drafting of the manuscript: Barete, Mouawad, and Francès. Critical revision of the manuscript for important intellectual content: Barete, Mouawad, Choquet, Viala, Leblond, Musset, Amoura, Khayat, and Francès. Statistical analysis: Barete and Mouawad. Obtained funding: Mouawad. Administrative, technical, and material support: Barete. Study supervision: Barete, Leblond, and Francès.

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REFERENCES


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Articles of Faith, Variant Acne

This little creature is composed of various articles that have been recommended in folk and traditional medicine for the treatment of acne. For the tail, we have toothpaste; for the body, oatmeal; for the legs, milk of magnesia; and for the ears, goat’s milk, all meant for topical use. The horns are cucumbers, which can be applied topically or taken internally as a juice. The eyes are complex: the centers are Pepto-Bismol tablets; around them are peppermints (which can also be used externally or internally); and the fuzzy cotton balls surround the mints can be used to apply any number of local agents, such as lemon juice, egg whites, neem oil, or witch hazel. The head is an antique urinal: a “duck” in medical parlance. Some authors advocate washing the face with urine to clear up the complexion, but given the choice between piss and pimples, I personally would opt for acne.

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