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Adenopathy and extensive skin patch overlying plasmacytoma syndrome—the clue to early diagnosis of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes: A case series and literature review

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Abstract

Importance: Adenopathy and extensive skin patch overlying plasmacytoma syndrome is a paraneoplastic syndrome characterized by a cutaneous vascular patch overlying a plasmacytoma and systemic manifestations. It is thought to be an early stage of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome, which is a rare, but potentially fatal multisystemic disease that is associated with plasma cell dyscrasia. Thus, a high index of suspicion is required to identify patients with adenopathy and extensive skin patch overlying plasmacytoma as they may present with early polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes, which is curable if detected early.
Objective: To report additional cases of adenopathy and extensive skin patch overlying plasmacytoma syndrome, describe dermatoscopic and histologic findings of the cutaneous patch and review all up to date literature on adenopathy and extensive skin patch overlying plasmacytoma syndrome.
Design: Case series from a single tertiary care center.
Participants: Here, we present the second case series of three patients with adenopathy and extensive skin patch overlying plasmacytoma syndrome who all meet the diagnostic criteria for polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. The diagnosis was suspected based on the presence of the violaceous cutaneous patch along with symptoms of systemic involvement (fatigue, weight loss, weakness). Dermoscopy revealing regular dilated parallel capillaries was suggestive of a benign/reactive vascular process. Histopathology in all three cases showed reactive vascular proliferation with a characteristic 90° branching. To date only 20 cases of adenopathy and extensive skin patch overlying plasmacytoma have been published, including ours. All patients presented with cutaneous lesions (violaceous patch and others) and most, at least 15/20, met the diagnostic criteria for polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. When clinical follow-up was reported, most patients had a favorable prognosis with partial or complete symptom resolution following treatment of the underlying plasmocytoma.

Keywords

adenopathy and extensive skin patch overlying plasmacytoma syndrome, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome, monoclonal gammopathy, plasmacytoma, violaceous patch, dermoscopy

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Introduction

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome is a rare disease associated with plasma cell dyscrasia.[1] While its pathogenesis is not completely understood, in up to 95% of cases, a λ light chain clone can be identified.[1] Clinical manifestations of POEMS syndrome are thought to result from an aberrant expression of inflammatory cytokines and growth factors produced by plasma and/or other cell types.[2] Due to its progressive nature and frequent delay in diagnosis, POEMS results in significantly impaired quality of life primarily owing to progressive polyneuropathy and because of multisystem involvement it is associated with poor survival.

Adenopathy and extensive skin patch overlying plasmacytoma (AESOP) syndrome is very rare and thought to represent an early stage of POEMS.[3] It is characterized by an underlying plasmacytoma which induces a violaceous vascular patch in the overlying skin and regional ipsilateral lymphadenopathy.[3] In contrast to POEMS, in AESOP, systemic complications are less common (e.g. endocrinopathy) and cure rates are higher.[3–5] Therefore, timely recognition of AESOP is important. To date, only 17 cases of AESOP have been published as either a single patient case report or small case series. Although it was hypothesized that AESOP may be an early stage POEMS syndrome, additional reports are warranted. Here, we present the second case series of three patients diagnosed with AESOP syndrome who all meet the criteria for POEMS syndrome and review all the current literature on the clinical presentation, evolution, and management of this disease. In addition, we report for the first time the dermoscopic features of the violaceous patch classically seen in AESOP and mention the histopathologic clue to the diagnosis. Written informed consent was obtained from all three patients.

Case 1

A 63-year-old female presented with a tender right thoracic violaceous patch that had appeared 1.5 years ago (Figure 1(a)); dermoscopic evaluation showed regular branching linear vessels suggestive of benign vascular lesion reminiscing of a telangiectasia (Figure 1(b)). One year after her initial visit, she developed an asymptomatic right axillary lymphadenopathy, lower limbs weakness, 15% weight loss, and hypothyroiditis. Additional features of physical examination at that time revealed facial lipoatrophy, diffuse hyperpigmentation of the upper and lower limbs, and sclerodermoid changes on her hands (Figure 1(c)). A 3 cm × 2 cm enlarged right axillary lymph node and other smaller (1 cm × 1 cm) lymphadenopathies were found. A neurologic exam corroborated by an electromyography with nerve conduction study (EMG) demonstrated polyneuropathy with demyelinating features. Papilledema of bilateral eyes and mild thrombocytosis (528 × 103 platelets/μL) were present. Histologic features of the skin biopsy revealed a benign vascular proliferation with a characteristic 90° angle branching of capillaries reminiscing of dermoscopic findings (Figure 2(b)); human herpes virus-8 (HHV8) was stain negative, and CD34 was positive (Figure 2(b)). Lymph node biopsy demonstrated angiofollicular hyperplasia indicative of Castleman's disease. Cerebrospinal fluid (CSF) analysis showed slightly elevated proteins. Serum protein electrophoresis and immunofixation confirmed a monoclonal IgG lambda chain peak. A computerized tomography (CT) scan of the chest wall revealed an osteolytic lesion on the seventh right rib (Figure 1(d)), histology of which was consistent with a plasmacytoma. The patient received cyclophosphamide, dexamethasone, and thalidomide and underwent surgical excision of the plasmacytoma.

Six months post-treatment, the patient recovered her original weight and the violaceous patch disappeared, but polyneuropathy persisted. One year later, a stem cell transplant was performed, and the patient reported improvement of paresthesia 6 months later.

Case 2

A 38-year-old male was referred for a 1-year history of lower limb paresthesia and weakness causing inability to walk and 10% weight loss. He also complained of a new violaceous patch on his right upper chest (Figure 2(a)). Physical examination demonstrated diffuse hyperpigmentation of the skin and mucosae, facial lipoatrophy, hypertrichosis, acral sclerodermoid changes, pseudo-leukonychia (Terry's nails), and lower limbs edema. A 20 cm × 15 cm erythematous ill-defined violaceous patch was seen on the right upper chest accompanied by ipsilateral cervical lymphadenopathy. Dermoscopy was similar to the first case. Neurologic examinations confirmed muscle atrophy, weakness, and generalized hyporeflexia. Papilledema was found on ophthalmoscopy. Laboratory investigations showed erythrocytosis (19.2 g/dL), thrombocytosis (372 × 103 platelets/μL), elevated erythrocyte sedimentation rate (ESR) (20 mm/h), and thyroid-stimulating hormone (TSH) (8 uUI/mL). Skin biopsy of the violaceous patch was identical to the first case (benign vascular proliferation, HHV8−, CD34+) (Figure 2(b)). Similarly, cervical lymph node biopsy was compatible with Castleman's disease and EMG documented mixed demyelinating polyneuropathy. Monoclonal peak and sternal plasmacytoma were confirmed by serum immunofixation electrophoresis and imaging, respectively.

Treatment with cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP) chemotherapy was initiated, followed by cyclophosphamide, dexamethasone, and thalidomide. Six months later, the patient recovered his original weight, the violaceous patch disappeared, and the upper and lower limb weakness improved. One year after treatment, the patient was able to walk again.

Case 3

A 64-year-old man presented with a 12 cm × 17 cm abdominal violaceous patch (Figure 3(a)), weight loss and lower limb weakness. Dermoscopy revealed a benign vascular pattern similar to the first two cases. Skin biopsy from the

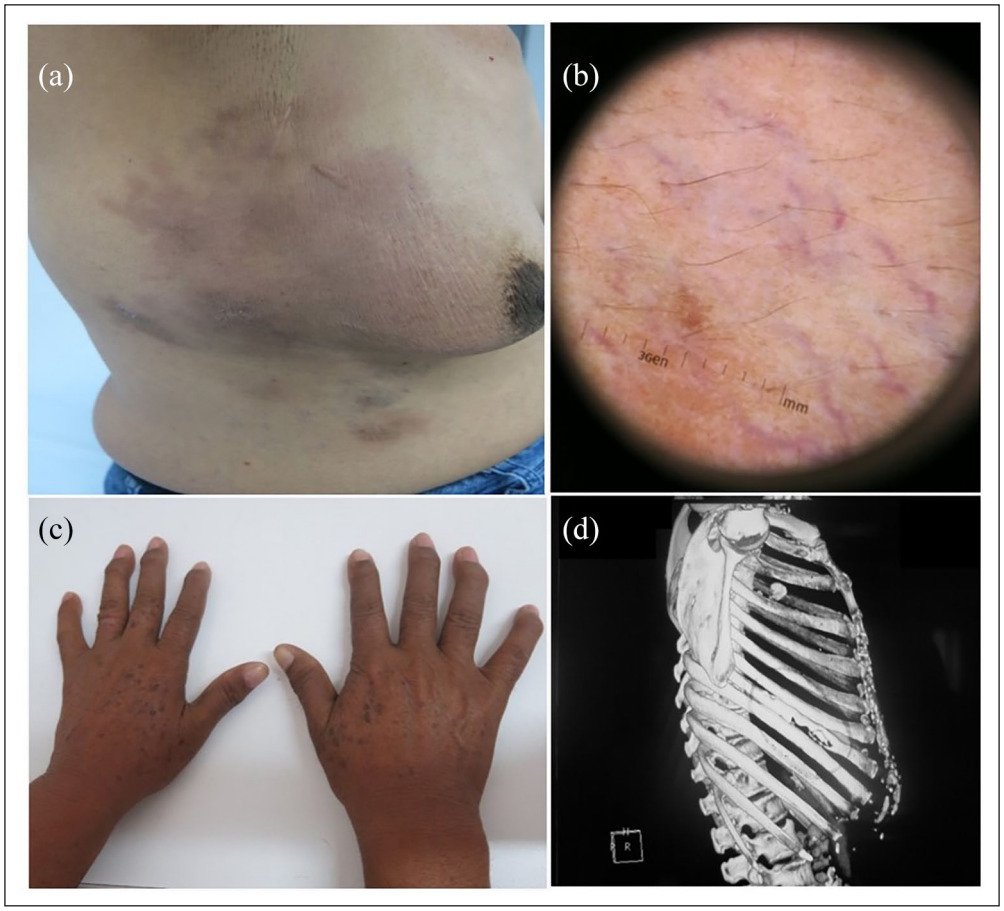

Figure 1. Patient #1: (a) extensive ill-defined right breast violaceous patch; (b) on dermoscopy using 10× polarized light, a regular pattern of parallel linear wavy/sinusoidal vessels was seen; (c) in addition to hyperpigmented macules, skin thickening with flexion contracture at the distal interphalangeal level was seen; (d) a plasmocytoma was found in the intercostal space on computed tomography.

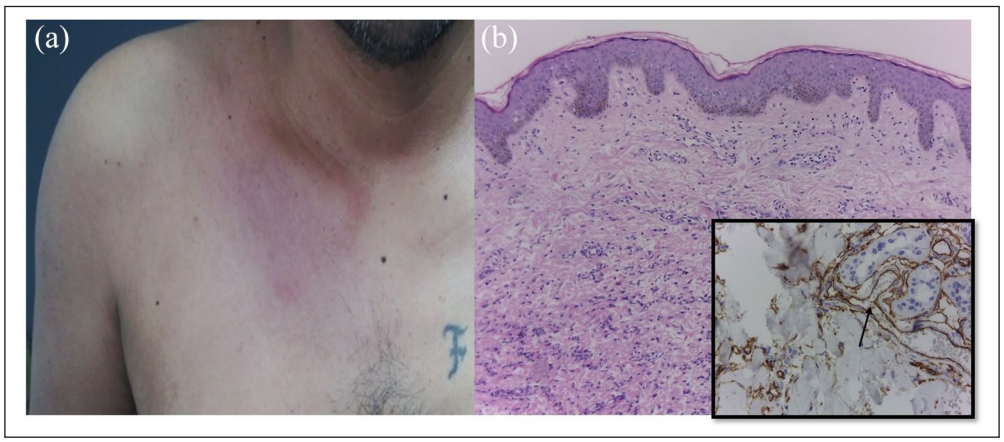

Figure 2. Patient #2: (a) ill-defined large erythemato-violaceous patch in the right clavicular area. The histopathologic features of this and two other cases demonstrated a regular proliferation of small blood vessels with a 90° branching (arrow) without any nuclear atypia or pleiomorphism; (b) stain for human herpes virus 8 was negative. CD34 stain was positive (close-up).

violaceous patch showed similar features to previous cases. Other cutaneous features included diffuse hyperpigmentation, hypertrichosis, facial lipoatrophy, and small scattered violaceous papules on trunk (Figures 3(b)). While the dermoscopic features of these papules were indistinguishable from cherry angiomas, histopathogic examination confirmed glomeruloid hemangiomas (Figure 3(c) and (d)). Left axillary lymphadenopathy and lower limb neuropathy were present.

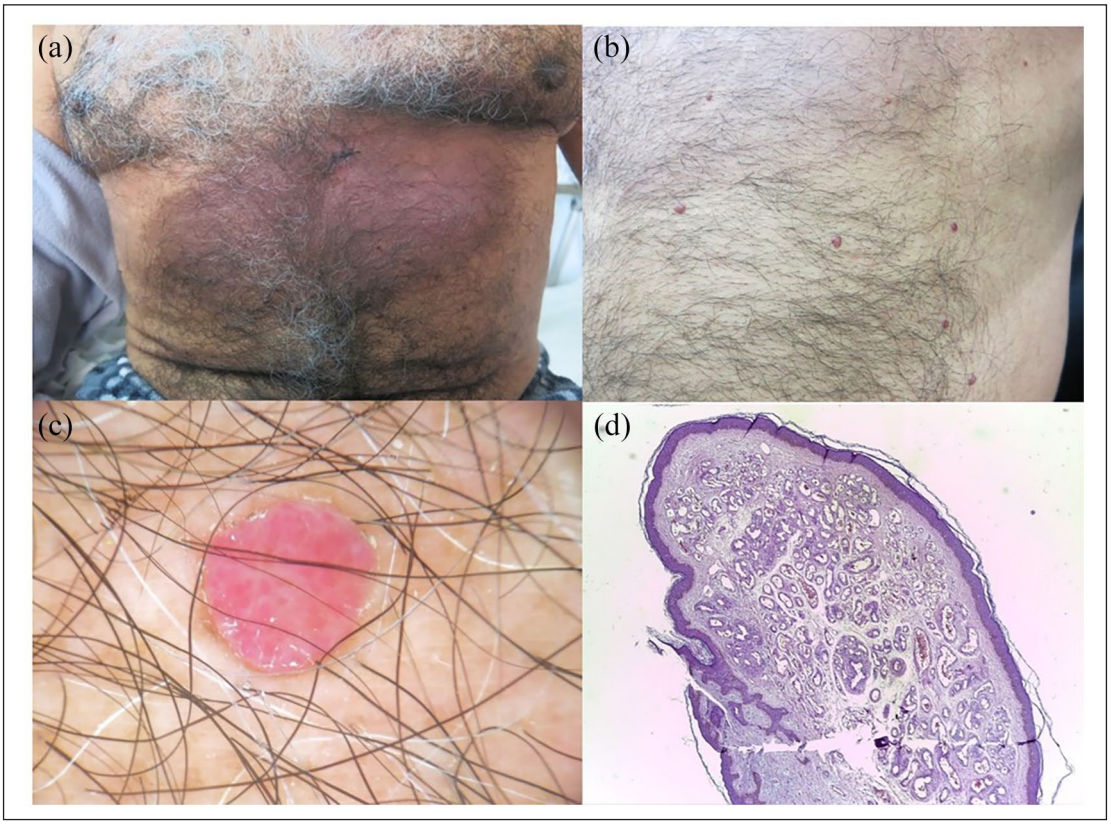

Figure 3. Patient #3: (a) extensive oval shaped violaceous patch extends from the chest to abdomen area; (b) small 2–4 mm red-violaceous papules can be seen on the right of the patch, similar lesions scattered on the trunk, limbs, and face; (c) dermoscopy using a 10× magnification showing red lacunae similar to those seen in cherry angioma; (d) biopsy of one of these papules demonstrates numerous ectatic vascular spaces, some resembling renal glomeruli and thereby confirming the suspicion of glomeruloid hemangiomas.

Distal hyporeflexia was found in the upper and lower limbs. A complete blood count was performed and revealed erythrocytosis (16.2 g/dL), thrombocytosis (565 × 103 platelets/μL), elevated ESR (25 mm/h), and TSH (7.7 uUI/mL). Similar to previous cases, the lymph node biopsy confirmed Castleman's disease, mixed demyelinating polyneuropathy was seen on the EMG, mild protein elevation was demonstrated on the CSF analysis, and ℵ-chain IgG monoclonal gammopathy and plasmacytoma were documented (6 cm × 2.5 cm osteolytic lesion on the fifth left rib).

Discussion

AESOP syndrome is rare and typically characterized by an erythematous-violaceous skin patch located on the thorax overlying a plasmacytoma and enlarged ipsilateral lymph nodes.[6] The skin patch is thought to originate from the chronic inflammatory process caused by the malignancy located underneath it. Vascular growth factors such as vascular endothelial growth factor (VEGF) induce a benign proliferation of blood vessels in the overlying dermis, which are readily seen on skin biopsy.[2,6]

AESOP syndrome may involve extracutaneous organs and/or tissues. Most commonly affected systems are lymph nodes featuring changes compatible with Castleman's disease and peripheral nerves with demyelinating polyneuropathy.[1] The cause of systemic manifestations is not well understood but is thought to result from the proinflammatory state with chronic release of inflammatory cytokines and growth hormones such as VEGF.[1] In addition to driving vascular skin changes, VEGF might cause or worsen neuropathy through unknown pathways.[6]

AESOP is thought to be by some as a variant and by others as an early manifestation of POEMS syndrome. A diagnosis of POEMS syndrome requires the presence of polyneuropathy and monoclonal plasma cell proliferation, plus the presence of at least one other major criterion, and one minor criterion.[1] Major criteria consist of an osteosclerotic or mixed sclerotic/lytic lesion on plain films or CT scan, Castleman's disease, and elevated serum or plasma VEGF levels of at least 3–4 times the upper limit of normal. Minor criteria include organomegaly, extravascular volume overload, endocrinopathy (excluding diabetes mellitus or hypothyroidism), skin changes, papilledema, and thrombocytosis or polycythemia.[7]

To date, 20 cases of AESOP syndrome have been published, including ours (Table 1).[3–6,8–17] In all cases, patients presented with an extensive ill-defined violaceous patch on

Table 1. Summary of reported cases of adenopathy and extensive skin patch overlying plasmacytoma (AESOP) syndrome.

Study	Age	Sex (M/F)	Neuropathy	Monoclonal plasma cell proliferation	*Major diagnostic criteria for POEMS*	*Minor diagnostic criteria for POEMS*	Diagnostic of POEMS	Treatment	Clinical outcome
Sheinker et al., 1938[3]*	39	M	+	NR	Plasmocytoma (sternum)	Lymphadenopathy Skin changes	+ (if considering plasmocytoma as a monoclonal plasma cell disorder)	None	Died within 1 year
Crow, 1956[17]	54	M	+	−	Plasmocytoma (scapula)	Lymphadenopathy Volume overload Skin changes	+ (if considering plasmocytoma as a monoclonal plasma cell disorder)	Radiotherapy	Lost to follow-up
Gupta et al., 1974[11]	18	M	+	+	Plasmocytoma (ribs)	Lymphadenopathy Volume overload Skin changes	+	Radiotherapy	Complete remission, but lost to follow-up
Read and Warlow, 1978[13]	58	M	+	−	Plasmocytoma (clavicle)	Lymphadenopathy Skin changes	+ (if considering plasmocytoma as a monoclonal plasma cell disorder)	Radiotherapy	Favorable
Feddersen et al., 1989[9]	42	M	+	+	Plasmocytoma (sternum) Castelman's disease	Lymphadenopathy Volume overload Skin changes Thrombocytosis and Polycythemia	+	Chemotherapy and Radiotherapy	Partial response
Weichenthal et al., 1999[16]	43	M	+	+	Plasmocytoma (skull) Castelman's disease	Lymphadenopathy Endocrinopathy Skin changes	+	Excision and radiotherapy	Complete remission
Lipsker et al., 2003[3]	66	M	+	+	Plasmocytoma (ribs)	Organomegaly/ lymphadenopathy Endocrinopathy Skin changes Papilledema	+	Excision	Died within 4 years
Lipsker et al., 2003[3]	73	M	NR	+	Plasmocytoma (sternum)	Lymphadenopathy Skin changes	−	Radiotherapy	Favorable
Lipsker et al., 2003[3]	34	M	+	NR	Plasmocytoma (ribs)	Skin changes	+ (if considering plasmocytoma as a monoclonal plasma cell disorder)	Radiotherapy	Favorable
Lipsker et al., 2003[3]	68	F	+	+	Plasmocytoma (sternum)	Organomegaly/ lymphadenopathy Endocrinopathy Skin changes	+	Excision and radiotherapy	Favorable

(Continued)

Table 1. (Continued)

Study	Age	Sex (M/F)	Neuropathy	Monoclonal plasma cell proliferation	*Major diagnostic criteria for POEMS*	*Minor diagnostic criteria for POEMS*	Diagnostic of POEMS	Treatment	Clinical outcome
Rongioletti et al., 2006[15]	64	F	−	+	Plasmocytoma (ribs)	Skin changes	−	Not known	Lost to follow-up
Foo et al., 2012[10]	53	M	NR	−	Sclerotic lesions, Blue-cell sarcoma with Ewing-like features, instead of a plasmacytoma	Lymphadenopathy Skin changes	−	Chemotherapy and radiotherapy	Complete remission, no evidence of disease recurrence at 6 years
Neel et al., 2012[12]	60	M	+	+	Plasmocytoma (ribs) Elevated VEGF	Organomegaly/ lymphadenopathy Volume overload Skin changes	+	Radiotherapy and chemotherapy	Favorable
Parker et al., 2013[4]	57	M	−	+	Plasmocytoma (ribs)	Lymphadenopathy Skin changes	−	Excision	Favorable
Cordero et al., 2014[8]	57	M	NR	+	Plasmocytoma (ribs)	Lymphadenopathy Skin changes	−	Excision and radiotherapy	Favorable
Rongioletti et al., 2016[14]	70	M	+	+	Plasmocytoma (ribs and spine) Castelman's disease	Organomegaly/ lymphadenopathy Volume overload Skin changes	+	Radiotherapy	Lost to follow-up
Dagrosa et al., 2019[5]	56	M	+	+	Plasmocytoma (ribs) Castelman's disease Elevated VEGF	Lymphadenopathy Volume overload Skin changes	+	Radiotherapy and chemotherapy	Favorable Partial resolution
Present study	63	F	+	+	Plasmocytoma (ribs) Castelman's disease	Lymphadenopathy Endocrinopathy Skin changes Papilledema Thrombocytosis	+	Chemotherap, surgery and stem cell transplant	Favorable
Present study	38	M	+	+	Plasmocytoma (sternum) Castelman's disease	Lymphadenopathy Endocrinopathy Skin changes Papilledema Thrombocytosis	+	Chemotherapy	Favorable
Present study	64	M	+	+	Plasmocytoma (ribs) Castelman's disease	Lymphadenopathy Endocrinopathy Skin changes Thrombocytosis	+	None	Lost to follow up

POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes; VEGF: vascular endothelial growth factor; NR: not reported.
Diagnostic criteria of POEMS include the presence of the *mandatory* criteria (e.g. polyneuropathy *and* monoclonal gammopathy) with at least *1 major* (e.g. Castleman disease, Sclerotic bone lesions, VEGF elevation) and *1 minor* criteria (e.g. organomegaly/lymphadenopathy, extravascular volume overload, endocrinopathy, skin changes, papilledema, and thrombocytosis/polycythemia).
*The original article (Sheinker I. Myelom und Nervensystem. Dtsch Z Nervenheilk 147: 247–73, 1938.) could not be retrieved, but case related information was available in Ref. 3 by Lipsker et al. (2003).

the trunk, in 19 an underlying plasmacytoma was identified, and in 1 case it was a blue-cell sarcoma.[10,15] The most common location of the plasmacytoma was ribs (10/19), followed by sternum (5/19), scapula (1/19), clavicle (1/19), skull (1/19), and cervical spine/ribs (1/19). Among 20 reported cases (including ours), 15 patients presented with polyneuropathy and 7 with Castleman's disease. Among all cases, considering the plasmocytoma as a monoclonal plasma cell proliferation, 15 patients (75%) explicitly met the criteria for POEMS. In an additional three cases, the presence of neuropathy was not reported and hence it is unknown if the diagnostic criteria would have been met. In only two cases including one case where the underlying tumor was a blue-cell sarcoma, neuropathy was absent and hence the diagnosis of POEMS could not be made. While most published cases did not specify the presence of most minor criteria for POEMS syndrome, papilledema was found in two-thirds of our patients in addition to one previously reported in the literature.[3] Furthermore, only select cases observed endocrinopathy (5/20) and organomegaly (4/20).[3,5,12,14] Lymphadenopathy and skin changes other than the violaceous patch were present in 18/20 and 20/20 patients, respectively. Unfortunately, most previous studies lack significant details regarding the management and prognosis. Nevertheless, most commonly reported treatment consisted of radiotherapy for the plasmacytoma alone or combined with either/or chemotherapy and surgical excision. While favorable response was mentioned in most cases, four patients were lost to follow-up and two succumbed to their disease and/or complications within 5 years of the diagnosis.

Given the significant overlap between AESOP and POEMS syndromes, we believe that AESOP should be recognized as a clinical manifestation of POEMS. Unifying AESOP as a clinical manifestation of POEMS would reduce confusion and help clinicians to better recognize and understand this condition. Having multiple names for the same/almost the same condition may cause a delay in the diagnosis and impact the prognosis. Unless a high index of suspicion for AESOP/POEMS, the patient's violaceous patch can be mistaken for a hematoma, an acquired vascular malformation or vascular neoplasms such as patch-stage Kaposi sarcoma or an angiosarcoma or even infectious causes, for example, erythema chronicum migrans. Although a skin biopsy may help to rule out other conditions, it will not provide the diagnostic confirmation and searching for plasma cell disease and associated features (e.g. neuropathy, endocrinopathy, and Castleman's disease) is essential. We report here for the first time the dermoscopic features of the violaceous patch that may help clinician to confirm the vascular nature and rule out the abovementioned conditions such as the dermoscopic appearance of Kaposi sarcoma (e.g. rainbow pattern and structureless areas) and angiosarcoma (e.g. atypical irregular vessels, structureless areas, and intersecting write lines) is different.[18,19] Early recognition of POEMS at the stage of AESOP syndrome is associated with a favorable outcome. We therefore suggest the endorsement of AESOP syndrome as a clinical manifestation of POEMS in order to improve diagnostic recognition and patient care. To avoid all confusion, clinicians should be aware that in addition to more common, but clinically nonspecific skin features seen in POEMS, such as cherry and glomeruloid hemangiomas, hyperpigmentation, hypertrichosis, hyperhidrosis, sclerodermoid features, plethora, acrocyanosis, white nails and flushing patients may present with a benign large truncal violaceous patch that is a clue to an underlying plasmacytoma.

In sum, this is the second case series to date of AESOP syndrome. Only 20 cases of AESOP have been reported to date including ours. The unique features of our series include the description of dermoscopic features of both the truncal vascular patch and glomeruloid hemangiomas that may help to rule out additional differential diagnoses. All our patients met the criteria for POEMS syndrome similar to 12/17 of previously reported cases. Given the significant overlap between AESOP and POEMS syndromes, we believe that AESOP syndrome should be recognized as a clinical manifestation of early POEMS. Unifying these conditions will allow for improved recognition, understanding, and management of these syndromes among clinicians with the ultimate goal to diagnose and treat at the curable stage of the disease.

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Informed consent

Written informed consent was obtained from all three patients for the publication of the details of their medical case and any accompanying photographic images.

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