Case Report

Intravascular B-Cell Lymphoma Presenting Solely with Generalized Telangiectasia on Normal-Appearing Skin: A Case Report

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Intravascular lymphoma is a rare type of lymphoma with a poor prognosis. Patients most often present with cutaneous or central nervous system findings. Its early diagnosis appears very important since it may be curable with appropriate chemotherapy regimens. A 61-year-old man who initially presented with diffuse arborizing telangiectasia on normal-appearing skin and limb edema is described. Skin biopsy and immunohistochemical studies confirmed intravascular B-cell lymphoma. After eight courses of treatment with combination chemotherapy (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone) the outcome was complete remission after an 18-month follow-up.

Keywords: Intravascular lymphoma, B-cell, Telangiectasia

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Intravascular lymphoma [IVL] is a rare disease with an usual fatal outcome, characterized by the proliferation within the lumen of small blood vessels of neoplastic large lymphoid cells of B-cell origin. Clinical presentation is often confusing, mimicking systemic disease. Diagnosis is difficult and often an autopsy finding. Prognosis is generally poor, but curable responses to appropriate chemotherapy have been observed after early diagnosis and treatment[1,2]. The authors report a patient with IVL of the skin who presented solely with generalized arborizing telangiectasia which is an uncommon cutaneous feature.

Case Report

A 61-year-old Thai man presented with generalized edema and multiple erythematous rash over both thighs and legs which had persisted for 6 weeks. He noted that his scrotum was swelling without evidence of inflammation. He also complained of low-grade fever without anorexia. He gained 10 kg of body weight during this period. No rheumatologic symptoms were reported. His past medical history was unremarkable without any history of hospitalization or major operations. He smoked at a 10 pack-year rate.

On physical examination, his vital signs were all within normal limits. His conjunctivae were pink, no icteric sclera was detected. There was no facial swelling or puffy eyelid. Heart and lungs were within normal limits. Neither hepatosplenomegaly nor an abnormal abdominal mass was palpated. Generalized swelling of both upper and lower extremities was identified. Cutaneous examination showed innumerable telangiectasia on the trunk, both upper and lower extremities with more the prominent on the thighs (Figure 1). On his abdomen and back, there were many brownish papules with a stuck-on appearance. No superficial lymphadenopathy was detected. His neurological examination was normal.

His blood chemistry showed blood urea

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nitrogen 13.7 md/dL, creatinine 1.1 mg/dL, cholesterol 155 mg/dL, albumin 3.1 g/dL, globulin 3.3 g/dL, alkaline phosphatase 180 U/L, lactate dehydrogenase 577 U/L. A complete blood count revealed mild anemia. The coagulogram was normal. D-dimer was 499 ng/mL. The HIV test was non-reactive. Ultrasonography of both legs showed no evidence of deep venous thrombosis. Ultrasonography of the scrotum showed scrotal swelling and mild hydrocele on both sides. Radionuclide lymphangiography of upper and lower extremities revealed no evidence of lymphatic obstruction. No lymphadenopathy of chest or abdomen was detected from the CT scan. Skin biopsy was performed from his left thigh. Sections of skin showed atypical medium to large cell aggregates in the lumen of small to intermediate size blood vessels. The cells showed medium to large nuclei with course nuclear chromatin and conspicuous nucleoli with scant cytoplasms (Figure 2). Immunohistochemistry studies which focused on the intravascular tumor cells revealed positives for LCA, CD20 (Figure 3), CD19, BCL-2 and BCL-6 and negatives for CD3, CD4, CD5, CD7, CD8, CD10, CD15, CD30, Granzyme B, and myeloperoxidase. Bone marrow biopsy showed normocellular trilineage marrow without abnormal cell aggregation. Intravascular B-cell lymphoma [IVL] presenting with generalized telangiectasia was diagnosed. The patient was treated with rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone for 8 courses. The outcome has been a complete remission after 18-month follow-up.

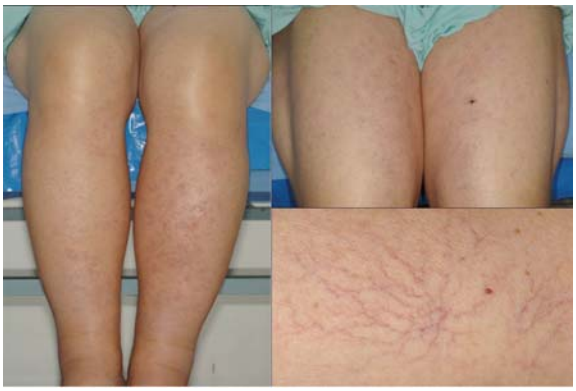

Figure 1. Generalized arborizing telangiectasia on lower extremities.

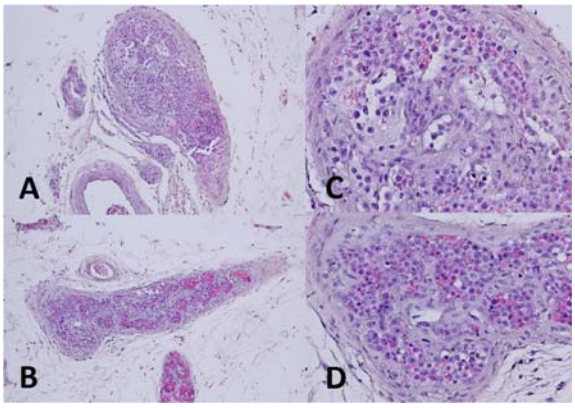

Figure 2. The section shows atypical cells aggregate in the lumen of blood vessels (A and B). The cells show medium to large nucleus with course nuclear chromatin and conspicuous nucleoli with scant cytoplasm (A and B) (hematoxylin-eosin stain, A and B x10; C and D x40).

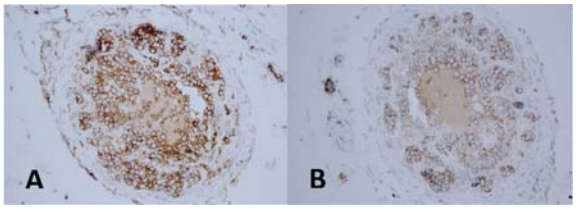

Figure 3. Immunohistochemistry studies show neoplastic cells positive for LCA (A) and CD20 (B) (x40).

Discussion

There are many acquired conditions that can present with generalized telangiectasia such as venous hypertension, generalized essential telangiectasia, autoimmune connective tissue diseases (lupus erythematosus, dermatomyositis, CREST syndrome/systemic sclerosis), mycosis fungoides including poikilodermatous, B-cell lymphomas, angiolupoid sarcoidosis, GVHD in the context of poikiloderma, HIV infection (anterior chest), liver disease, carcinoid syndrome and mastocytosis (telangiectasia macularis eruptiva perstans; TMEP)[1]. A complete history taking and physical examination can help to narrow differential diagnoses and make a proper investigations. This patient presented with generalized telangiectasia and generalized edema along with low-graded fever. The differential diagnosis included venous hypertension due to venous obstruction, hematologic malignancies such as TMEP and lymphoma and autoimmune connective tissue diseases. After full investigation, there was no evidence of deep venous thrombosis by ultrasonography of both legs. Connective tissue

diseases were a less possibility due to lack of rheumatologic symptoms and the negative results of serologic tests for autoimmune disease. The absence of chronic liver stigmata made liver disease unlikely. These suggested that hematologic malignancies were more likely. Furthermore, histopathological findings and immunohistochemical studies from the lesion from the left thigh confirmed the diagnosis of intravascular lymphoma [IVL].

IVL is a rare type of extranodal non-Hodgkin lymphoma which is characterized by proliferation of lymphoma cells within the lumen of small to medium-sized vessels. It usually, however, lacks lymphoma cells in the reticuloendothelial system and lymph nodes until late in the disease and relative sparing of the parenchyma of involved organs. It has many historical names such as angioendotheliomatosis proliferans systemisata, malignant angioendotheliomatosis, intravascular lymphomatosis, angio-endotheliotropic (intravascular) lymphoma and angiotropic large cell lymphoma[2,3]. Advanced immunohistochemical studies clearly demonstrated that the intravascular tumor cells expressed markers of hematopoietic cells and were not of endothelial cell origin. Most of the cases involved are of B-cell lineage, so intravascular large B-cell lymphoma is a reasonable term. About 90% of reported cases of IVL are large B-cell lymphoma, and only 10% to 15% of IVL are of T-cell lineage. Patients usually present with multifocal neurological deficits, skin rashes or fevers. Patients with skin changes are discovered earlier in the course of the disease because of the widespread use of the skin biopsy whereas patients presenting solely with neurological symptoms tend to elude the diagnosis more frequently[2].

The skin manifestation is a common presentation in IVL. Because of the striking heterogenicity of the cutaneous features, however, IVL can mimic a variety of diseases. Frequencies of skin involvement are variable between 0 to 60% depending on each series of patients[3]. In the largest series, Ferreri JM, et al reported that cutaneous lesions were the predominant presenting feature in 15 of 38 cases (39%)[3]. While Murase T, et al. reported a series of 96 patients with intravascular large B-cell lymphoma and found that cutaneous lesions were noted in 14 patients (15%)[4]. Roglin J and Boer A had reviewed 97 articles reporting on total of 224 patients with IVL and found that skin lesions were mentioned in 90 patients (40%)[5]. Common locations in decreasing order of frequency are thigh (41%), leg (35%), trunk (31%), arm (15%) and buttock (7.5%). Most commonly skin lesions were nodules and/or plaque (49%), followed by induration (27.5%), macules (22.5%) and telangiectasia (20%). Telangiectasia is a rare presentation of IVL[6,7]. In a Japanese series, there was only 1 of 9 patients in which teleangiectasia was the presentation[8]. In cases presenting with telangiectasia, most of the cases presented with indurated telangiectatic plaques but only presented with diffuse telangiectasia on the normal-appearing skin rarely (Table 1)[9-16]. There were only three cases of IVL, however, that presented with generalized edema of extremities along with diffuse telangiectasia on the normal-appearing skin as in the present case[11,13,15]. Skin manifestations of IVL may mimic inflammatory skin diseases depending on the level of vascular involvement; for example, if subcutaneous vessels are involved, they may mimic an indurated nodule from panniculitis[6]. Importantly the other differential diagnosis of telangiectasia is IVL.

The mechanism of telangiectasia is thought to be a reactive vascular proliferation to the thrombo-occlusive insult caused by the intravascular proliferation[9]. So telangiectasia are evidence of recanalization and of recurrences of lesions at the very same site[6]. In the same way, the possible mechanism of edema is thought to result from infiltration of large neoplastic lymphocytes into lumina of blood vessels, leading to vascular occlusion[13]. Because massive proliferation of large tumor cells occur within the lumina of small to medium-sized vessels, ultrasonography which can detect only obstruction in large vessels, may show negative results as in the current case.

About two thirds of cases present with neurological symptoms including mental status changes, dementia, peripheral neuropathy, radiculopathy, myelopathy, stroke, encephalitis and CNS vasculitis, however, these usually are misdiagnosed because of no pathognomonic neuroradiological findings for IVL[2]. Common manifestations of IVL other than skin manifestation include fever, general fatigue, neurologic symptoms, gastrointestinal symptoms, dyspnea and edema. Although any organ can be involved, liver, spleen, lymph nodes and bone marrow are relatively spared until late in the disease. Typically lymphoma cells are not seen circulating in the peripheral blood or cerebrospinal fluid[6]. A rare but fatal complication is hemophagocytic syndrome which is more common in Asian countries[7]. There is usually absent lymphadenopathy. Although IVL is typically a B-cell lymphoma, there are rare cases of T-cell origin and

Table 1. Summary of IVL presenting with diffuse telangiectasia on the normal-appearing skin

Case No.	Age (year)	Sex	Skin manifestation	Systemic involvement	Phenotype	Treatment	Follow-up	Reference
1	60	F	Generalized telangiectasia, violaceous infiltrated plaques	-	B cell	CHOP regimen	Not improved	9
2	73	F	Generalized telangiectasia	Stroke, encephalopathy	B cell	Combination chemotherapy	Died	10
3	64	F	Diffuse superficial telangiectasia, edema on the lower limbs and trunk	Cauda equina syndrome, hemophagocytic syndrome	B cell	Combination chemotherapy	Died without evidence relapse of IVL	11
4	79	F	Generalized telangiectasia, edema and orange-like skin	Multiple lacunar brain infarction, hepatomegaly	B cell	PUVA, chlorambucil, CHOP, rituximab	Complete remission	12
5	79	M	Diffuse telangiectasia, lower-limb edema	Repeated superficial venous thrombosis, abdominal pain, deterioration in performance status	B cell	CHOP, rituximab	Good	13
6	58	M	Generalized telangiectasia and pitting edema	Hepatosplenomegaly	B cell	-	Died from sepsis	14
7	79	F	Diffuse telangiectasia on breasts and trunk, pitting edema of legs and trunk	-	B cell	-	Died from multiorgan failure	15
8	75	F	Diffuse telangiectasia,abdominal subcutaneous edema	-	B cell	NA	NA	16
The present study	61	M	Generalized telangiectasia, edema of extremities	-	B cell	CHOP, rituximab	18 months; alive	

F = Female; M = Male; IVL = intravascular lymphoma; CHOP = cyclophosphamide/adriamycin/vincristine/prednisolone; PUVA = psoralen with ultraviolet A; NA = Not available

natural killer and histiocyte variants have been identified.

The histopathological differential diagnosis of intravascular cellular proliferation includes reactive angioendotheliomatosis, an intravascular proliferation of endothelial cells secondary to occlusion[14] or inflammation of vascular lumina and intravascular/intralymphatic histiocytosis associated with various inflammatory and neoplastic diseases[17].

The diagnosis of IVL is difficult due to the variation of presentations. Organ biopsies are mandatory for the accurate diagnosis. Skin is the diagnostic material in 7 of 13 patients with IVL in one series[8]. If the patient has a skin lesion, the target is a visible skin lesion. But if there are skin lesions detected, a random skin biopsy which includes the hypodermic adipose tissue is also useful[12]. Prognosis of IVL is very poor; if left untreated, it is usually fatal. Patients with neurological and systemic symptoms at presentation typically have a poor prognosis, probably related to the delay in diagnosis compared with skin only involvement[2].

For disseminated B-cell lymphoma, most authors advocate an anthracycline-based chemotherapy regimen with the addition of the anti-CD20 monoclonal antibody, rituximab. This combination can induce complete remission with a survival advantage. There are case reports in the literature of sustained remission after using rituximab as a single modality. Localized cutaneous lesions have been treated successfully with local radiation therapy[2,6,18].

Conclusion

The authors describe an interesting cutaneous presentation of intravascular lymphoma that was an uncommon feature. Early diagnosis and an appropriate therapy made the disease curable with a favorable prognosis.

What is already known in this topic?

The skin manifestation is a common presentation in IVL and can mimic a variety of diseases.

What this study adds?

Generalized telangiectasia on the normal-appearing skin is a rare manifestation of IVL.

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Potential conflicts of interest

The authors declare no conflict of interest.

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