Intravascular lymphoma presenting with paraneoplastic syndrome

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Abstract

Intravascular lymphomatosis (IVL) is a rare type of B-cell non-Hodgkin lymphoma (BCNHL), which can mimic many other diseases. Fever, neurological symptoms, and skin findings are the most frequent clinical findings. Intravascular lymphomatosis may be associated with genetic factors and infection with human immunodeficiency virus (HIV), human herpesvirus 8 (HHV-8), human T-lymphotropic virus 1 (HTLV1), Epstein-Barr virus (EBV), and hepatitis B virus (HBV). A 50-year-old man was hospitalized with recalcitrant hyponatremia of unknown cause. He had also telangiectatic, indurated, slightly erythematous plaques on his trunk for the last 10 days. His past medical history was unremarkable, although he was a carrier of hepatitis B. Multiple skin biopsies were performed and were considered to be diagnostic of IVL. The hyponatremia was unresponsive to water restriction and hypertonic solution support but it resolved with B cell directed chemotherapy. A final diagnosis was made as syndrome of inappropriate antidiuretic hormone (SIADH) in the setting of IVL. This case had a relatively early diagnosis with just 10-days of skin lesions. Intravascular lymphomatosis is a very rare disease and is usually difficult to diagnose. An even more uncommon presentation is IVL complicated by a paraneoplastic syndrome. There are prior reported cases of SIADH in the setting of IVL. However, this case underscores the importance of evaluating patients with SIADH for potential IVL.

Keywords: intravascular, lymphoma; B-cell lymphoma, syndrome of inappropriate antidiuretic hormone, hepatitis-B, paraneoplastic

Case Synopsis

A 50-year-old man with recalcitrant hyponatremia and leg edema had been followed-up for 20 days in the department of nephrology during which time he developed diffuse erythematous patches of 10 days' duration, which necessitated a dermatology consultation. His past medical history was remarkable for the patient being a hepatitis B carrier.

Dermatological examination demonstrated multiple indurated, erythematous, widespread telangiectatic plaques on the trunk (**Figure 1A)** and legs. In addition, there were cigarette-paper-like atrophic plaques on the right abdominal wall and the lateral side of the trunk (**Figure 1B)**. He had generalized weakness and mild confusion. His laboratory parameters revealed anemia, hypochloremia, and hyponatremia. Hepatitis B and total anti-Hepatitis B core antigens were positive. Other routine blood tests were within normal limits.

Two skin biopsies were taken from the telangiectatic plaque and atrophic plaque. The biopsies appeared similar and demonstrated striking collections of intermediate to large atypical mononuclear cells occluding the vascular spaces throughout the dermis (**Figure 2**). The intravascular cells showed strong staining with CD20 and MUM-1 without significant immunoreactivity for bcl-2, bcl-6, CD3, CD5, CD10, or CD21 (**Figure 3**). A diagnosis was made of intravascular large B-cell lymphoma.

All the radiologic tests, peripheral blood smear, and bone marrow biopsy were within normal limits. Following three courses of chemotherapy there was

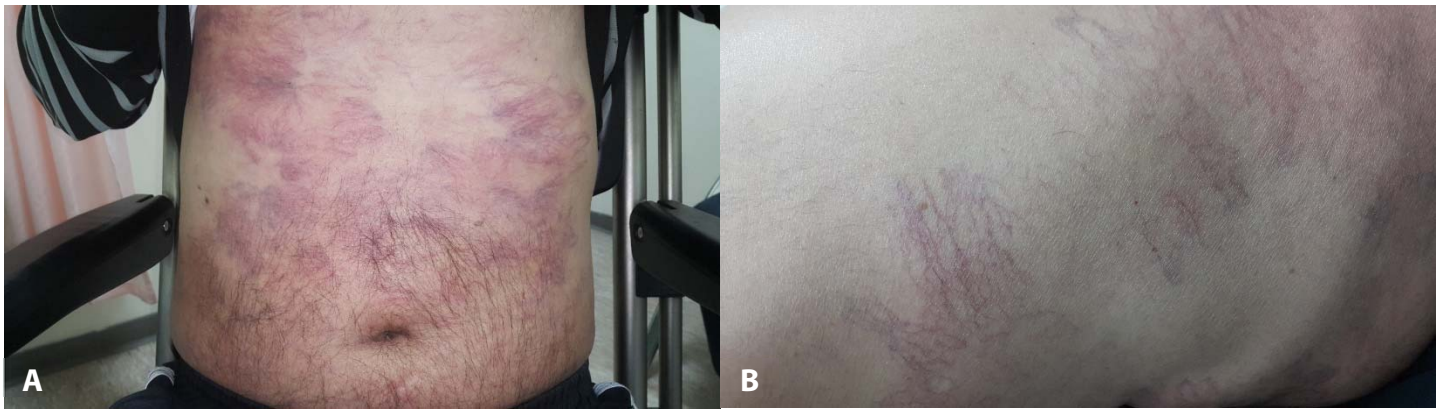

Figure 1. ***A)*** *Indurated and erythematous, widespread telangiectatic plaques on the abdomen.* ***B)*** *Cigarette-paper-like atrophic patches on the lateral side of the trunk.*

a significant improvement in the appearance of his skin and his electrolyte abnormalities resolved. He had 8 courses of chemotherapy to achieve complete remission and has been disease free for the last three years.

Intravascular lymphomatosis (IVL) is a rare type of lymphoma characterized by neoplastic lymphocytes growing within the vascular spaces. In most cases the intravascular lymphoma is of B cell lineage and represents a primary intravascular large cell B cell lymphoma. However, there are rare intravascular T cell variants and as well both nodal and extranodal T and B cell lymphomas that can exhibit an intravascular pattern of growth. In the primary intravascular B cell lymphoma setting, the central nervous system and the skin are most commonly affected whereas extravascular lymph node and bone marrow involvement would not be expected [1,2]. Intravascular lymphomatosis is found to be associated with HIV, HHV-8, HTLV1, EBV, monoclonal gammopathy, and genetic factors [3-5]. There were none of these associations in our case. However, there is literature data suggesting an association between HBV and BCNHL, in accordance with our case [6-8].

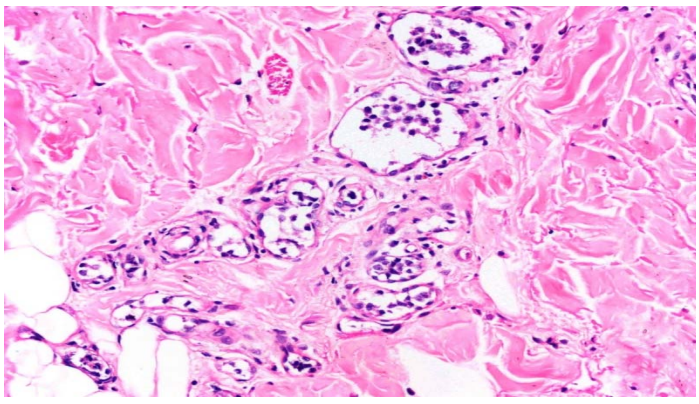

Figure 2. *Round cell groups in the deep dermal vascular spaces. H&E, 20×.*

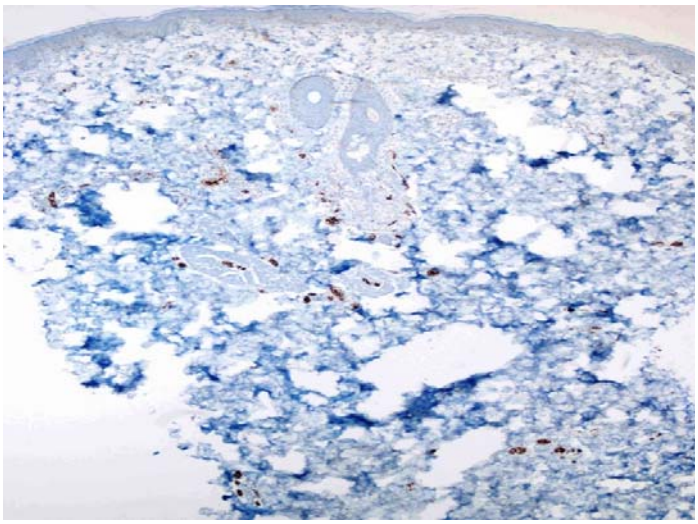

Figure 3. *Strong staining with CD20 in the vascular spaces, 4×.*

Fever of unknown origin, progressive neurologic signs and symptoms, weakness, loss of appetite, and skin changes are the most common symptoms [9]. In our case, the patient had resistant hyponatremia, which was unresponsive to water restriction and hypertonic solution support. A diagnosis was made of SIADH. It was paraneoplastic in nature owing to the concurrent IVL and the resolution following treatment of the lymphoma. Similar cases have been reported in the literature. A summary of other cases of IVL and SIADH are found in **Table 1** [10]. An Asian variant of IVL (AIVL) is described as IVL with

Table 1. *Syndrome of inappropriate antidiuretic hormone in intravascular lymphomatosis patients reported in the literature.*

Reference	Age	Gender	IVL type	Organ involvement	SIADH	Treatment	Outcome
Akthar et al. (2013), [10]	75	Male	IVL	Lungs, kidneys, adrenal glands and pituitary gland	Concurrent	None	Died of disease
Namikawa et al. (1995), [11]	66	Male	IVL	Brain, lungs, kidneys, adrenal glands, spleen and pancreas	Concurrent	None	Died of disease
Watabe et al. (2000), [12]	70	Male	AIVL	Liver, pulmonar artery, pituitary gland	Concurrent	Pirarubicin, cyclophosphamide, vincristine, prednisone, and etoposide Post-mortem diagnosed	Died of disease
Onishi et al. (2011), [13]	73	Female	AIVL	N/A_	N/A_	N/A_	N/A
Onishi et al. (2011), [13]	80	Male	AIVL	N/A_	N/A_	N/A_	A/A
Onishi et al. (2011), [13]	83	Male	AIVL	N/A_	N/A_	N/A_	N/A_
Onishi et al. (2011), [13]	69	Male	AIVL	N/A_	N/A_	N/A_	N/A_
Morimoto et al. (2007), [14]	75	Male	IVL	Liver, lung, adrenal glands, kidneys, stomach, gallbladder, thymus, prostate,	Preceding	None	Died of disease

AIVL, Asian variant of intravascular lymphomatosis; IVL, intravascular lymphomatosis; SIADH, syndrome of inappropriate antidiuretic hormone. N/A, not available.

hemophagocytic syndrome and hypercytokinemia. Onishi et al. showed that AIVL patients are at a higher risk to develop SIADH compared to other lymphoma patients [13]. According to the data in the **Table 1**, there is a male predominance with many of the cases representing the AIVL variant [13].

The mechanism of SIADH in the setting of lymphoma is unclear but various mechanisms have been proposed including excess antidiuretic hormone secretion from lymphoma cells, involvement of central nervous system and endocrine glands, or chemotherapy [10,12,13]. Some authors also focus on elevated serum IL6, which is produced by activated T cells and macrophages. There is also evidence that IL6 stimulates antidiuretic hormone secretion in the hypothalamus when administered by the intravenous route [13,14].

Conclusion

Owing to the cutaneous presentation a diagnosis was made of IVL relatively early in this patient's clinical course. This early diagnosis allowed critical and life-saving therapeutic interventions. In any patient with the constellation of an altered mental status, refractory hyponatremia, and skin findings the syndromic complex of SIADH in the setting of IVL should be considered.

Informed Consent: An informed consent has been received from the patient to be able to share his pictures and his medical data in scientific meetings and journals.

Potential conflicts of interest

The authors declare no conflicts of interests

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