Eruptive Telangiectasia as a Presenting Manifestation of Intravascular NK-cell Lymphoma: a Rare Case Report and Review of the Literature.

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ABSTRACT:

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Intravascular NK-cell lymphoma (IVNKL) is a very rare neoplasm. Although intravascular B-cell lymphoma is recognized as a common variant of mature B-cell neoplasm, IVNKL has not even been categorized by the World Health Organization (WHO) classification. To date, a few cases of IVNKL have been reported. The most common presentation is erythematous patches and plaques on trunk and extremities. Only a single case presented with blanching erythematous patches that resemble telangiectasia.

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Here, we report a case of IVNKL presented with eruptive telangiectasia, papules and plaques on the upper trunk and extremities accompanied with progressive weight loss. Skin histopathology showed atypical mononuclear cell infiltrations within lumina of blood vessels. Immunohistochemical study revealed NK cell phenotype with PCR and DNA sequencing for EBV were positive.. Thorough investigations were done and showed no internal organ involvement. Treatment was started with prednisolone. Unfortunately, the patient passed away 2 months after the diagnosis because of tumor lysis syndrome.

Key words : Telangiectasia, Intravascular lymphoma, NK-cell lymphoma, Epstein-Bar virus

บทคัดย่อ :

อาภาศรี สุขสำราญ ปุณวิศ สุทธิกุลณเศรษฐ์ รายงานผู้ป่วยที่มีการเกิดภาวะเส้นเลือดฝอยขยายตัวผิดปกติอันเกิดจากมะเร็งต่อมน้ำเหลืองภายในหลอดเลือดชนิด NK เซลล์ วารสารโรคผิวหนัง 2560; 33: 275-285.

สถาบันโรคผิวหนัง กรมการแพทย์ กระทรวงสาธารณสุข

มะเร็งต่อมน้ำเหลืองภายในหลอดเลือดชนิด NK เซลล์ พบมีรายงานน้อยมาก และยังไม่ถูกจัดหมวดหมู่โดยองค์การอนามัยโลก ในขณะที่ มะเร็งต่อมน้ำเหลืองภายในหลอดเลือดชนิด B เซลล์จัดอยู่ในกลุ่มมะเร็งต่อมน้ำเหลืองชนิด B เซลล์ คนไข้มักมีอาการแสดงเป็นผื่นราบหรือผื่นนูนหนาสีแดง ที่ลำตัวและแขนขา จนถึงปัจจุบัน มรายงานเคนไข้ มะเร็งต่อมน้ำเหลืองภายในหลอดเลือดชนิด NK เซลล์เพียงรายเดียว ที่มาด้วยภาวะเส้นเลือดฝอยขยายตัวผิดปกติบริเวณผิวหนัง

ในที่นี้ ได้รายงานผู้ป่วยโรคมะเร็งต่อมน้ำเหลืองภายในหลอดเลือดชนิด NK เซลล์ ที่มาด้วยอาการแสดงของภาวะเส้นเลือดฝอยขยายตัวผิดปกติ รวมทั้งมีผื่นที่เป็นตุ่ม และผื่นนูนหนาสีแดง ที่ลำตัวและแขนขา บริเวณผิวหนัง ร่วมกับมีน้ำหนักลด การส่งชิ้นเนื้อเพื่อการวินิจฉัย ทางจุลพยาธิวิทยาพบว่ามีเซลล์เม็ดเลือดขาวชนิดโมโนนิวเคลียร์ที่มีลักษณะผิดปกติอยู่ภายในหลอดเลือด การศึกษาทางอิมมูโนพยาธิวิทยาพบว่าเซลล์ที่ผิดปกติ เป็นเซลล์เม็ดเลือดขาวชนิด NK และพบเชื้อไวรัส เอ็บสไตบาร์ หรือย่อว่า อีบีวี จากการส่งตรวจพิเศษด้วยวิธีเทคนิคพอลิเมอเรสเชนรีแอชันหรือพีซีอาร์ จึงให้การวินิจฉัยคนไข้รายนี้ว่าเป็นมะเร็งต่อมน้ำเหลืองภายในหลอดเลือดชนิด NK เซลล์ ซึ่งระยะที่พบยังไม่มีการกระจายของมะเร็งดังกล่าวสู่อวัยวะภายใน คนไข้เริ่มรักษาโดยยาทานเพรดนิโซโลน อย่างไรก็ตาม คนไข้เสียชีวิตในเวลา 2 เดือนหลังจากวินิจฉัย สาเหตุอันเนื่องจากเกิดภาวะแทรกซ้อนจากการสลายของเซลล์ มะเร็งจำนวนมาก(tumor lysis syndrome)

คำสำคัญ : ภาวะเส้นเลือดฝอยขยายตัวผิดปกติ โรคมะเร็งต่อมน้ำเหลืองภายในหลอดเลือด
มะเร็งต่อมน้ำเหลืองชนิด NK เซลล์ เชื้อไวรัส เอ็บสไตบาร์

Case report

A 38 year-old male, with known underlying dyspepsia presented with asymptomatic eruptive red rashes over his trunk and upper extremities for 2 months, accompanied with fatique and 9 kilograms of weight loss in 1 month.

On physical examination, he had high grade of fever (BT 38.3°C). No hepatosplenomegaly or lymphadenopathy was detected. Other examinations were unremarkable.

Dermatological examination showed bilateral, symmetrical, multiple telangiectasia with some indurated erythematous papules and plaques involving the upper trunk, extremities, nape of his neck, lower abdomen and lower back. Neither skin atrophy nor Darier's sign was observed **(Figure 1)**.

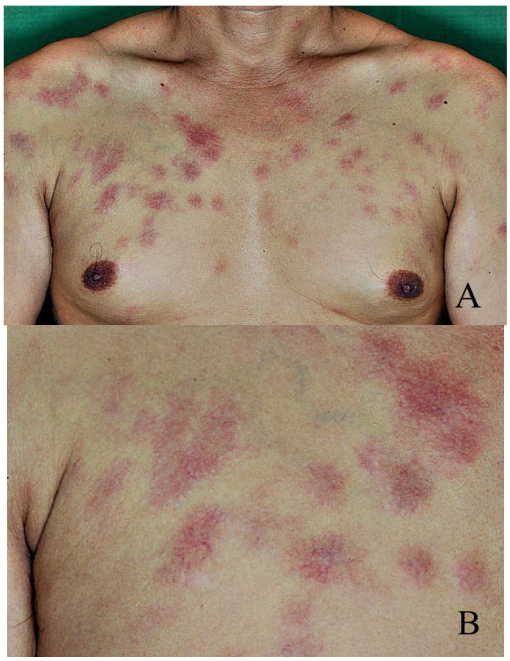

Figure 1 Dermatological examination showed bilateral, symmetrical, multiple telangiectasia with some indurated erythematous papules and plaques involving the upper trunk**.**

Further investigations were done and showed normal basic laboratory results (complete blood count, liver and renal function tests). Lactate dehydrogenase level (LDH) was elevated (1011 U/L; normal = 207-414).

Skin biopsy was done from indurated papule on upper trunk and showed normal epidermis with superficial perivascular lymphocyte infiltrations. There was a distinct infiltration by mononuclear cells with enlarged hyperchromatic nuclei within lumen of blood vessels in mid to deep dermis **(Figure2)**.

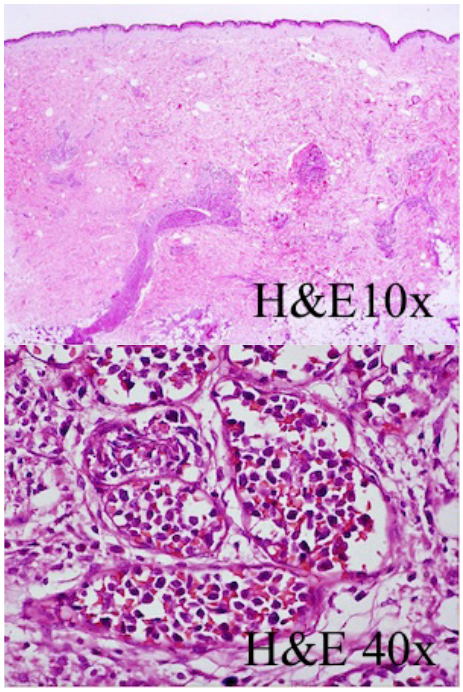

Figure 2 Histological examination showed distinct infiltration by mononuclear cells with enlarged hyperchromatic nuclei within lumen of blood vessels**.**

Immunohistochemistry was done. The majority of tumor cells was CD3+, CD4-, CD5-,

CD8-, CD56+, CD68+, CD30-, CD20- ,granzyme B+ and myeloperoxidase+ **(Figure3).** Most tumor cells nuclei were Ki-67 positive. Multiplex polymerase chain reactions for T-cell receptor (TCR) gene analysis showed polyclonality. PCR and DNA sequencing with Sanger method were positive for Epstein-Barr virus type1.

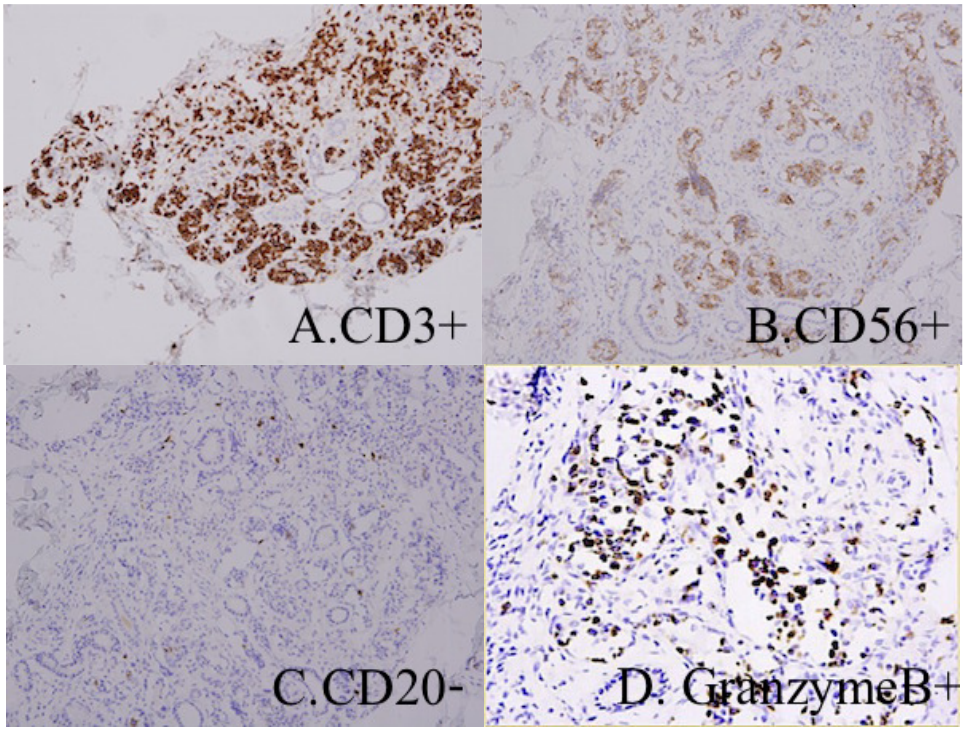

Figure 3 Immunohistochemistry showed majority of tumor cells was CD3+, CD56+, CD20- and granzyme B+

All the histopathologic findings and immunohistochemistry stains were compatible with IVNKL. CT-scan of chest and abdomen revealed no internal organ involvements. Bone marrow biopsy also showed no malignancy cells.

The patient was received treatment with prednisolone 30 mg/day for 1 months, nevertheless no improvement was observed. He was planned to start CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimen. Unfortunately, the patient passed away 2 months after the diagnosis due to tumor lysis syndrome.

Discussion

Intravascular lymphoma is a rare disease characterized by the presence of atypical cells within lumina of vessels, especially capillaries. The most common cellular immunophenotype of intravascular lymphoma is B-cell phenotype, which is recognized as a variant of mature B-cell

neoplasm by the 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia.[1] About 27 cases of published literatures are T-cell variants and the rarest phenotype is intravascular NK-cell lymphoma (IVNKL).[2]

Skin manifestations can present around 40% of patients with IVL. The cutaneous presentations are varies, including nodules/plaques (49%), induration (27.5%) and macules (22.5%) with red, blue or grey to brown colored.[4] The lesions usually presents on thighs, followed by legs and trunk, respectively.[4] Telangiectasia is found about 20% of the IVL patients.[4] However, only a single case of IVNKL has been reported as presenting with telangiectasia and painful skin lesions.[5]

All the previous reported cases of IVNKL were summarized in **Table 1**. Most of the case reports were from Asian populations (China, Taiwan, Korea and Japan). Our case is the first case of IVNKL from Thailand.

More than haft of the reported cases had associated symptoms which were fever (52%), weight loss (24%), fatique and malaise (19%), and chills (10%). Central nervous system (71%) and bone marrow involvement (28%) were the most common internal organs involvements, followed by kidney, ovary, cervix, and spleen involvements (Table 1).

The typical histopathologic features are the presence of mononuclear cells with enlarged hyperchromatic nuclei within lumina of blood vessels in dermis and subcutaneous tissues. None of the tumor cells breaks through perivascular zone. Immunophenotypes are shown in **Table 2.** The tumor cells usually reveal CD56+, cytotoxic marker+ (Perforin, Granzyme B and TIA1), CD3+, CD4-, CD5-, CD8-, CD20- and CD30-. EBV were detected in most of the cases as shown in **Table 2**. Only one case had a negative test result for EBV by both in situ hybridization studies for EBV encoded RNA(EBER) and polymerase chain reaction technique for EBV DNA.[6]

The mainstay of the treatment is CHOP regimen. Other regimens such as CODOX-M, IVAC, ProMACE/CytaBOM, L-ASP, EPOCH and hyperCVAD have been reported. Stem cell transplantation had successful outcome in a single case report.[6] Only 4 out of 21 cases survived more than one year (Table 1). All the alive cases had no internal organ involvement[6,9-11] (Table 1). Three cases survived during the short follow-up period (range from 2-7 months)[12-14] (Table 1). The rest were death with various causes including CNS involvement, acute-graft-versus-host disease, multi-organ failure, and from the disease itself.

Most of the death cases had initially presented with either systemic symptoms or internal organ involvement. Our case is the first

case of IVNKL that initially showed high LDH and died from tumor lysis syndrome which may be precipitated by prednidolone.[15, 16]

Telangiectasia is one of various clinical manifestation of IVNKL. Abrupt onset of telangiestasia, indurated papules, plaques and nodules accompany with systemic symptoms may use as a clue for the suspicious of IVL.[17,18] The skin biopsy and immunohistochemical study is necessary for early diagnosis, and prompt treatment.

Table 1 Twenty-one reported cases of IVNKL

NO.	Age/ Sex	Source	Cutaneous manifestation	Associate findings	Internal organ involvement	Treatment	Follow-up	Alive/ Death	Ref.
1.	54/M	Italy	Erythematous plaque on trunk and thighs	Weight loss (LDH: not reported)	CNS	CHOP	17 mo.	D[CNS involvement]	7
2.	41/M	USA	Asymptomatic erythematous plaques lesion on lower extremities and thigh	No (LDH: not reported)	No	CHOP and SCT	1 yr.	A	6
3.	47/F	USA	No	Myalgia, arthralgia, weakness , fever, confusion (LDH: not reported)	CNS, bone marrow, kidney, ovaries, cervix	NA	15 days	D	6
4.	71/F	Taiwan	Pruritic erythematous patches and nodule on trunk and extremities	No (LDH: not reported)	No	No treatment	5 mo.	A	12
5.	40/F	Korea	Non pruritic erythematous plaque on whole body	Dysphasia and right-side weakness (LDH: not reported)	CNS	CODOX-M and IVAC	7 mo.	A	13
6.	23/F	Japan	Erythematous plaque on abdomen, leg oedema	Fever (LDH: not reported)	Spleen P	CHOP,ProMACE /CytaBOM, L-ASP/CY,hyperCVAD/ MTX-AraC, related SCT	9 mo.	D [aGVHD]	3

NO.	Age/ Sex	Source	Cutaneous manifestation	Associate findings	Internal organ involvement	Treatment	Follow-up	Alive/ Death	Ref.
7.	63/M	Austria	Infiltrated red-violaceous plaques on trunk and extremities	Weight loss, fever, asthenia and depression (LDH: not reported)	No	CHOP	6 mo.	D	19
8.	68/F	China	Erythematous patches and nodules on trunk and extremities	Fever (LDH: not reported)	NA	L-ASP/BAM/ VDs./MP	2 mo.	D	8
9.	22/M	China	Erythematous patches and nodules on trunk and extremities	Fever (LDH: not reported)	NA	CHOP-L	2 mo.	D	8
10.	42/F	Taiwan	Tender erythematous indurated plaque on lower extremities and thighs	Malaise, dizziness and chilly sensations (LDH: not reported)	No	RT, CHOP, bortezomib, EPOCH	14 mo.	A	9
11.	65/F	China	Erythematous patches on both lower limbs	Fever, chilly sensation and malaise (LDH: not reported)	No	Deny chemotherapy	4 mo.	A	14
12.	72/M	Germa n	Nonpruritic erythematous plaque on trunk and extremities	No (LDH: not reported)	CNS and bone marrow	Chlorambucil+ urbasone, intrathecal MTX	7 mo.	D[sepsis]]	21
13.	38/F	China	Subcutaneous erythematous plaque on chest and back	Intermittent fever (LDH: not reported)	CNS	CHOP	13 mo.	D	22
14	29/M	China	Painful blanching irregular erythematous patches on trunk, lower and upper extremities	Low fever, headachesand weight loss , leukopenia (LDH: not reported)	Liver	hyperCVAD	3 mo.	D [multi-organ failure]	5
15.	45/M	China	Erythematous macule and plaques on trunk and thigh	Malaise , fever, weight loss (LDH: not reported)	NA	NA	2 weeks	D	10

NO.	Age/ Sex	Source	Cutaneous manifestation	Associate findings	Internal organ involvement	Treatment	Follow-up	Alive/ Death	Ref.
16.	52/F	China	Painful subcutaneous macules and plaques on her thigh	No (LDH: not reported)	NA	CHOP	6 mo.	D	10
17.	32/M	China	Erythematous patches	Fever (LDH: not reported)	No	CHOP	4 mo.	D	10
18.	18/F	China	Painful erythematous macule and plaques on lower extremities	No (LDH: not reported)	No	CHOP	3 yr.	A	10
19.	51/M	China	Erythematouspatc hes on back and thigh	Fever, weight loss, abdominal pain (LDH: not reported)	No	CHOP+VP-16	6 mo.	D	10
20.	48/F	Saudi Arabia	Erythematous patches and nodules on lower extremities	No. (LDH: not reported)	No	Chemotherapy not defined	18 mo.	A	11
21.	38/M	Thai [our case]	Erythematous telangiectatic patches with telangiectatic indurated papules and plaques on upper trunk and upper extremities	Weight loss, Fatique (LDH elevated)	No	Prednisolone[p lan for CHOP]	2 mo.	D[tumor lysis syndrome]	

M, male; F, female; NA, not available; D,dead; A, alive; EBV, Ebstein-Barr virus; CNS, central nervous system; aGVHD, acute graft-versus-host disease SCT, stem cell transplant; RT, radiotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CODOX-M, cyclophosphamide, vincristine, doxorubicin and methotrexate; IVAC, ifosfamide, mesna, etoposide and cytarabine; ProMACE/CytaBOM, prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytosine arabinoside, bleomycin, vincristine, leucovorin; L-ASP, L-asparaginase; CY, cyclophosphamide; hyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; MTX, methotrexate; AraC, cytosine arabinoside; EPOCH, etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin

Table 2 Immunophenotypes of previous case reports

NO.	Immunophenotypes								EBV	PCR-TCR	Ref.
	CD56	Cytotoxic marker	CD3	CD4	CD5	CD8	CD20	CD30			
1.	+	+	+	-	NA	-	-	+	+	NA	7
2.	+	+	+	-	-	-	-	-	+	P	6
3.	+	+	+	-	-	-	-	NA	-	P	6
4.	+	+	+	-	-	-	-	-	+	P	12
5.	+	+	+	-	-	-	-	-	+	P	13
6.	+	+	+	NA	NA	NA	-	NA	+	NA	3
7.	+	+	+	-	NA	-	-	NA	+	P	19
8.	+	+	+	NA	NA	NA	NA	NA	+	NA	8
9.	+	+	+	NA	NA	NA	NA	NA	+	NA	8
10.	+	+	+	-	-	-	-	-	+	NA	9
11.	-	+	+	-	-	-	-	-	+	P	14
12.	+	+	+	-	NA	-	-	-	+	P	21
13.	+	+	+	-	-	-	-	-	+	NA	22
14.	+	+	+	-	-	-	-	+	+	P	5
15.	+	+	+	-	NA	-	-	-	+	NA	10
16.	+	+	+	-	NA	-	-	-	+	NA	10
17.	+	+	+	-	NA	-	-	-	+	NA	10
18.	+	+	+	-	NA	-	-	+	+	NA	10
19.	+	+	+	-	NA	-	-	-	+	NA	10
20.	-	+	+	-	-	-	-	-	+	NA	11
21.	+	+	+	NA	NA	_	_	-	+	P	

P: polyclonal (no clonal T-cell population)

NA:non available

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