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Case Report

Primary hepatosplenic CD5-positive diffuse large B-cell lymphoma: a case report with literature review

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Abstract: *De novo* CD5-positive diffuse large B-cell lymphoma ($CD5^+$ DLBCL) accounts for approximately 10% of DLBCL, and is usually associated with aggressive clinical course. We report a case of $CD5^+$ DLBCL with primary involvement of the spleen and liver, and no distinct mass lesions or lymphadenopathy. The patient had stage IV disease with bone marrow involvement by lymphoma. The lymphoma cells showed characteristic portal and intrasinusoidal pattern of infiltrate in the liver. The literature was reviewed and the clinicopathologic features of 7 similar reported cases were summarized. All cases share the common features of hepatosplenomegaly without mass lesions, exclusive red pulp infiltrate with a diffuse and cordal pattern in the spleen, portal and intrasinusoidal pattern of infiltrate in the liver, and stage IV disease with poor response to conventional chemotherapy. This may represent a distinct subgroup of $CD5^+$ DLBCL and the diagnosis is important for prompt clinical treatment.

Keywords: CD5, diffuse large B-cell lymphoma, hepatosplenomegaly

Introduction

De novo CD5-positive diffuse large B-cell lymphoma ($CD5^+$ DLBCL) is uncommon, accounting for up to 10% of diffuse large B-cell lymphoma (DLBCL) [1]. *De novo* $CD5^+$ DLBCL has unique clinicopathologic features distinct from other DLBCL [2-6]. They are typically associated with old age, female predominance, more frequent bone marrow involvement, advanced stage, and higher International Prognostic Index score [6]. $CD5^+$ DLBCL has a poor prognosis with aggressive clinical course and responds poorly to conventional chemotherapy including regimen with rituximab [7-9]. Morphologically the $CD5^+$ DLBCL cells more often show intravascular or intrasinusoidal infiltration pattern. It has been noted that $CD5^+$ DLBCL is a heterogeneous group with a small subset showing primary and exclusive involvement of the spleen and liver [10]. However, the clinicopathologic features of this group of $CD5^+$ DLBCL with primary hepatosplenic involvement have not been well characterized. In this report, we present a case of an 80-year-old male with primary hepatosplenic $CD5^+$ DLBCL, and summarize the clinicopathologic features of similar cases in the literature.

Case report

An 80-year-old man with a history of hypertension, hyperlipidemia, chronic obstructive pulmonary disease, osteoarthritis and hepatitis as a child presented with recent onset of abdominal pain, fever, chills, sweats, nausea, decreased appetite, weight loss, malaise and lethargy. CT scan and X-ray showed hepatosplenomegaly, with no lymphanenopathy or extranodal mass lesions. The complete blood count (CBC) was normal. Liver enzyme studies showed mildly elevated aspartate aminotransferase (AST), alkaline phosphatase and bilirubin with a direct bilirubin of 0.4 mg/dL. Urinalysis was normal and blood culture was negative. The patient was temporarily treated with ciprofloxacin and acetaminophen with no improvement in symptoms. Esophagogastroduodenoscopy and subsequently liver biopsy were performed for diagnosis.

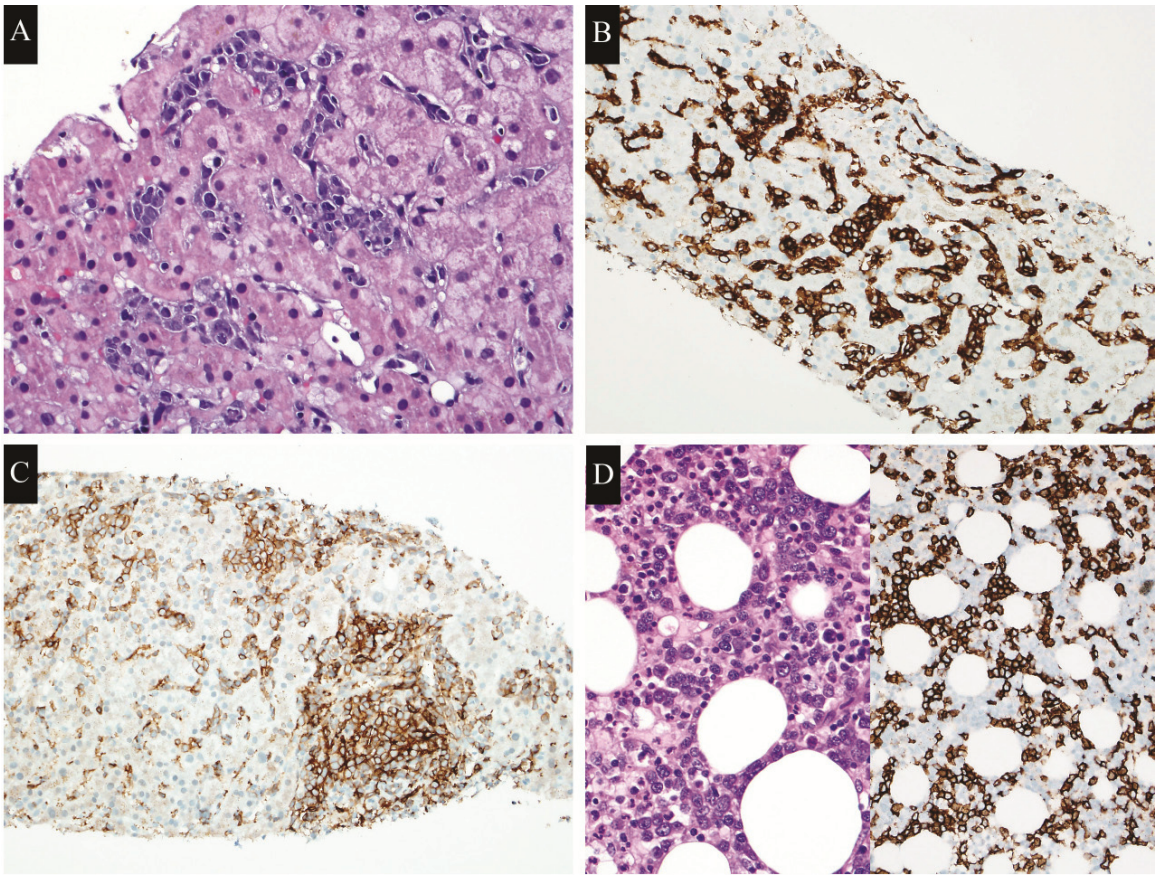

Figure 1. Primary hepatosplenic CD5-positive diffuse large B-cell lymphoma. A. Liver biopsy, hematoxylin-eosin stain, magnification 400x. B. Liver biopsy, CD20 immunostain, magnification 200x. C. Liver biopsy, CD5 immunostain, magnification 200x. D. Bone marrow biopsy hematoxylin-eosin stain (left panel, magnification 400x), and CD20 immunostain (right panel, magnification 200x).

The liver biopsy showed portal and intrasinusoidal infiltrate of large atypical lymphoid cells with round nuclei, open chromatin and prominent nucleoli (**Figure 1A**). By immunohistochemical stains, the large atypical lymphoid cells were positive for CD20 (**Figure 1B**), CD79a, PAX5, and BCL6, and showed co-expression of CD5 (**Figure 1C**). They were negative for CD10, MUM1, Cyclin D1 and CD23. Ki-67 showed high proliferation rate of the neoplastic B-cells with approximately 80% positive cells. EBV-encoded RNA in-situ hybridization (EBER) was negative. The findings were diagnostic of CD5-positive DLBCL. Bone marrow biopsy was performed for staging and revealed extensive involvement by $CD5^+$ DLBCL in an interstitial infiltrating pattern (**Figure 1D**), occupying approximately 50% of the marrow space. Flow cytometry of the bone marrow aspirate showed a population of kappa restricted monoclonal B-cells with co-expression of CD5, supporting the marrow involvement by $CD5^+$ DLBCL.

Discussion

Literature review showed 7 additional cases of *De novo* $CD5^+$ DLBCL with primary hepatosplenic involvement [10-12]. In addition, Yamaguchi et al reported 13 similar cases among 109 cases of *De novo* $CD5^+$ DLBCL, but no detailed description specifically for the 13 patients [6]. The clinicopathologic features of the 7 cases were summarized in **Table 1**. All 7 patients were elderly male with an age range from 64 to 81 years (median, 68 years). All patients had stage IV disease (**Table 1**) with involvement of the spleen (7 cases), liver (5 cases), bone marrow (4 cases) and peripheral blood (3 cases). Lymphadenopathy was absent, except in one case with localized lymphadenopathy. The *De novo* $CD5^+$ DLBCL cells showed splenic red pulp infiltrate in diffuse and cordal pattern. Intrasinusoidal infiltrate could be seen in some cases. The liver biopsies showed portal and intrasinusoidal infiltrate by lymphoma

Table 1. Primary hepatosplenic CD5-positive diffuse large B-cell lymphoma in the literature

RF	Cases	Age/ Sex	Extranodal sites	Stage	Infiltration Pattern		Immunophenotype							Therapy	Outcome
					Spleen	Liver	CD20	CD5	CD23	CD10	BCL6	MUM1	Cyclin D1		
Kroft et al. [10]	2	M/68	S, L, BM	IV	Red pulp D & C	Portal ISI	+	+	_	_	NA	NA	_	CHOP	DOD
		M/64	S, L, PB	IV	Red pulp D & C	ISI	+	+	_	_	NA	NA	_	NA	NA
Kong et al. [12]	1	M/65	S, L, BM	IV	NA	NA	+	+	_	_	NA	NA	_	CHOP	DOD
Kashimura et al. [11]	4	M/75	S, L, BM, PB	IV	Red pulp D, C, ISI	Portal ISI	+	+	_	_	_	_	_	CHOP-R	Alive
		M/68	S, L, BM	IV	Red pulp D, C, ISI	Portal ISI	+	+	_	_	+	+	_	CHOP	DOD
		M/70	S	NA	Red pulp D, C, ISI	NA	+	+	_	+	_	+	_	CHOP	Alive
		M/81	S, PB	IV	Red pulp D, C, ISI	NA	+	+	_	_	_	_	_	CHOP	DOD

RF, reference; M, male; F, female; S, spleen; L, liver; BM, bone marrow; PB, peripheral blood; D, diffuse; C, cordal infiltrate; ISI, intrasinusoidal; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; R, rituximab; DOD, dead of disease; NA, not available.

cells. The lymphoma cells were positive for CD20 and CD5, and negative for cyclin D1. The two cases reported by Kroft et al had no surface or cytoplasmic immunoglobulin expression [10], while 4 cytogenetic and/or FISH studies performed in 5 cases were negative for t(11;14)(q13;q32) or IGH-Cyclin D1 gene rearrangement [12]. CD10 was positive in only one of 7 cases, and BCL6 was positive in 2 of 4 cases tested. Based on expression of CD10, BCL6, and MUM1 in 4 cases, there were 1 GCB, and 3 non-GCB subtypes based on Han's algorithm. All cases were negative for Epstein-Barr virus when tested by EBER. The clinical course was aggressive with poor response to chemotherapy; 4 patients died of the disease after chemotherapy with CHOP based regimen, and only 2 patients were alive after treatment.

CD5 is a 67-kd T-cell surface glycoprotein typically co-expressed by chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and occasionally other small mature B-cell lymphomas. The function of aberrant expression of CD5 in small mature B-cell neoplasm is uncertain. However, in diffuse large B-cell lymphomas not evolving from small mature B-cell lymphomas, the co-expression of CD5 is uncommon at about 10% of the cases. The *de novo* $CD5^+$ DLBCL usually has a more aggressive clinical course and poor prognosis. Kroft et al observed that the *de novo* $CD5^+$ DLBCL represented a heterogeneous group with some cases resembling CLL or MCL [10]. Of note, a subset of the *de novo* $CD5^+$ DLBCL showed more unique clinicopathologic features with predominant involvement of the spleen and liver, diffuse splenic red pulp involvement and distinct cordal pattern of infiltrate.

We report a case of *de novo* $CD5^+$ DLBCL with primary hepatosplenic involvement, and a distinctive pattern of portal and intrasinusoidal infiltrate in the liver. Clinicopathologic features of 7 similar cases in the literature were summarized. These cases shared the same distinctive clinicopathologic features, including hepatosplenomegaly without dominant mass lesions, absence of other mass lesions such as lymphadenopathy, exclusive red pulp infiltrate with a diffuse and cordal pattern in the spleen, portal and intrasinusoidal pattern of infiltrate in the liver, and stage IV disease with involvement of the bone marrow and peripheral blood. The cordal and intrasinusoidal distribution of lymphoma cells in the spleen and liver differ from typical mass lesions and/or white pulp infiltrate of diffuse large B-cell lymphoma, including those transformed from CLL/SLL. The phenotype of the lymphoma cells (CD20+CD5+CD23-) was against CLL/SLL. Blastoid MCL was excluded by negative cyclin D1 expression and absence of t(11;14)(q13;q32) or IGH-Cyclin D1 gene rearrangement by cytogenetic or FISH studies. None of the cases had previous history of CLL/SLL, MCL or other small mature B-cell lymphoma. The intrasinusoidal pattern also raised the possibility of intravascular large B-cell lymphoma (IVLBCL). But the reported $CD5^+$ IVLBCL was negative for splenomegaly,

and the typical symptoms of IVLBCL including neurologic symptoms, pancytopenia and hemophagocytic syndrome were absent. Clinically these cases showed aggressive clinical behavior with 4 of the 6 patients died of the disease shortly after chemotherapy. Whenever liver biopsies were available, the liver was always involved by splenic $CD5^+$ DLBCL with characteristic portal and intrasinusoidal pattern of infiltrate. Hence, these primary hepatosplenic $CD5^+$ DLBCL cases may represent a subcategory of $CD5^+$ DLBCL with distinct clinicopathological features and prompt diagnosis is essential in regard to management.

There are additional cases of diffuse large B-cell lymphoma reported in the literature with splenomegaly and predominant red pulp infiltrate in the spleen. There were 2 cases reported by Arber et al [13], 2 cases by Palutke et al [14], one case by Salgado et al [15], and 13 cases by Yamaguchi et al [6]. However, these cases lacked detailed description of clinicopathologic features or immunophenotypic findings. It is presumed that all these cases represented the same disease category.

CD5 is expressed in a heterogenous group of B-cells including transitional B-cells, and pre-naïve B-cells in human. A subset of normal B-cells expressing CD5 (B-1a cells) was found in rodent and they comprise the majority of B-cells in fetal spleen and cord blood, and only a small subset of adult peripheral blood B-cells. Adult spleen also contains a small percentage of B-1a cells. Human B-cells with same function of mouse B-1a cell have been proposed. These B-cells are positive for CD20, CD27, and CD43, but negative for CD70. Kroft et al reported 2 cases of CD5+ DLBCL with immunoglobulin negative phenotype, while in the four cases reported by Kashimura et al, the $CD5^+$ DLBCL cells of three cases tested had IgM but not IgD [11], which are similar to the phenotype of B-1a cells. Hence, the primary hepatosplenic $CD5^+$ DLBCL cells could be derived from splenic transitional or pre-naïve B-cells, which may explain the predominant and exclusive involvement of spleen and liver, and tendency to circulate in the peripheral blood with subsequent bone marrow involvement.

In summary, *de novo* primary hepatosplenic $CD5^+$ DLBCL may represent a distinct clinicopathologic subcategory of $CD5^+$ DLBCL. It almost always is a stage IV disease with an aggressive clinical course. Recognition of this disease entity is important clinically for prompt diagnosis and therapy. The presence of B-symptoms and weight loss should alert the clinician of the possibility of primary hepatosplenic lymphomas, including $CD5^+$ DLBCL, despite no discrete mass in an enlarged liver or spleen by imaging studies. Given the high frequency of bone marrow involvement, either a bone marrow biopsy or liver biopsy with corresponding flow cytometric and immunohistochemical studies will direct to the correct diagnosis. The poor response of previous cases to conventional chemotherapy (CHOP) necessitates additional studies for optimal treatment.

Authors' disclaimer

The authors indicated no potential conflicts of interest.

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