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Increased CD5 positive polyclonal B cells in Castleman disease: a diagnostic pitfall

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Sir

CD5+ B lymphocytes (B1 lymphocytes in the mouse) comprise a large proportion of B cells during early fetal life but decrease with age. They produce polyreactive antibodies and have been implicated in autoimmune disease, including rheumatoid arthritis, Sjogren's syndrome, and systemic lupus erythematosus.¹ Castleman disease also has been associated with autoimmune disorders.² CD5 expression on B cells of the expanded mantle zones in Castleman disease has been reported in sporadic cases, and was mainly associated with the plasma cell variant.^{3, 4} However, most of these reports are from the older literature, and employed frozen section immunohistochemistry. Additionally, in some of the reported cases molecular studies identified clonal immunoglobulin gene rearrangements, raising the possibility of involvement by a CD5+ B-cell lymphoma.⁴ With the recognition that patients with monoclonal B-lymphocytosis (MBL) can have limited lymph node involvement,⁵ ruling out early involvement by MBL or chronic lymphocytic leukemia becomes of paramount importance. Similarly, CD5+ B-cells in the *in situ* form of mantle cell lymphoma can be confined to the lymphoid cuff.⁶

We sought to determine if CD5+ B-cells were expanded in Castleman disease, and if such cases were associated with monoclonal B-cell expansion. Fifteen cases (Castleman disease, hyaline vascular variant (13); plasma cell variant (2) were collected from NCI hematopathology consultation service between 2010 and 2012, and screened for CD5 expression on mantle zone B cells by immunohistochemical staining using both a rabbit monoclonal anti-CD5 antibody (SP19, Abcam, Cambridge, MA, USA) and a mouse monoclonal anti-CD5 antibody (4C7, Novacastra-Leica Biosystems, Buffalo Grove, IL, USA) (Table 1). The immunohistochemical panel also included immunostains for CD20, IgD, CD21, CD23, CD3, kappa, lambda, and cyclin D1. Cases of multicentric Castleman disease positive for HHV-8/KSHV were excluded. PCR analysis for immunoglobulin gene rearrangement was performed on all cases with detectable CD5 expression. Flow cytometric data was correlated with the morphologic findings when available.

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Author contributions:

Drs. Qingyan Liu and Elaine S. Jaffe reviewed all of the cases, and wrote the manuscript. Drs. Pittaluga, Raffeld and Xi were responsible for the immunohistochemical and molecular studies, and data analysis. Ms. Davies-Hill was responsible for collecting clinical and pathological data.

Six of the 15 cases showed evidence of CD5 positivity on mantle zone B cells by the CD5/SP19 antibody, but not by the CD5/4C7 antibody (Figures 1 and 2). All CD5+ positive were classified as the hyaline vascular subtype, although in one instance (Case 9), polyclonal plasma cells were prominent in the interfollicular region. The CD5+ B-cells were confined to the expanded mantle zones, and were also positive for IgD, but negative for cyclin D1 by immunohistochemistry. All of the 5 CD5+ cases tested were negative for clonal immunoglobulin gene rearrangement by PCR analysis. Four cases with flow cytometric data showed the B cells to be polyclonal.

Of the 6 cases with CD5 expression, 4 presented with a slowly growing localized mass lesion, but were otherwise asymptomatic. One patient had a history of thymoma and SSA antibodies indicative of autoimmune disease. Only one patient had more generalized lymphadenopathy, raising concern for lymphoma. The median age of the CD5-positive cases was 46 years, with a female predominance (M:F=1:2), whereas the median age of the CD5-negative cases was 37 years with a male to female ratio of 4:5.

Our study confirms that CD5 expression is a common feature of the B-cells in the expanded mantle zones of Castleman disease, and that this finding should not necessarily raise alarm for involvement by a CD5+ B-cell lymphoma. In addition, with greater use of the more sensitive rabbit monoclonal antibodies this phenomenon is likely to be more widely seen. Monoclonal antibodies prepared in rabbits have enhanced the detection of multiple antigens in tissue sections.⁷ In this small series we did not observe a definite correlation with autoimmune phenomena, although one CD5+ did have anti-SSA autoantibodies and a history of thymoma.

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Figure 1. Morphologic features of a lymph node diagnosed as the plasma cell variant of Castleman disease (case 9, LN). Follicles show broad, expanded mantle zones (A). The regressed follicles have penetrating vessels (B). Numerous plasma cells are present in the interfollicular area, shown at upper right. The plasma cells were polyclonal (not shown). The expanded follicles are positive for CD20 (C). The mantle zones are positive for CD5, while clusters of T-cells staining more strongly for CD5 are within the regressed germinal center and peripheral to the follicle (D).

Figure 2.

Morphologic features of a case of hyaline vascular variant of Castleman disease (case 10, Tonsil). The expanded follicles show “twining” with multiple regressed germinal centers within an expanded mantle zone (A). Lollipop appearance of a penetrating vessel (B). The follicles are positive for CD20 (C), with IgD highlighting the expanded mantle zone; note the negative IgD staining of regressed small germinal centers (D). The mantle zone is negative for CD3 (E), but positive for CD5 (F).

Table 1

Case#	Age/Sex	Site	Diagnosis	CD5 (SP19)	Cyclin D1	IG PCR	Clinical Features*
1	41/F	LN, axillary	HV-CD	-	-	NA	Axillary mass
2	44/F	LN, pelvic	HV-CD	-	NA	NA	Pelvic mass
3	15/F	LN, post. cervical	HV-CD	-	NA	NA	Slowly growing neck mass for years
4	21/M	LN, paratracheal	PC-CD	-	NA	NA	Fever, cough, chest tightness/paratracheal mass
5	22/F	LN, cervical	PC-CD	-	NA	NA	Multiple LN's, night sweats, weight fluctuation, SOB on exertion, polyclonal hypergammaglobulinemia, increased ESR
6	37/M	LN, inguinal	HV-CD	-	NA	NA	Inguinal, pelvic, paraaortic LN, lytic bone lesion
7	37/M	LN, mesenteric	HV-CD	-	-	NA	Mesenteric mass
8	63/F	LN, iliac	HV-CD	+	-	-	Iliac fossa mass
9	51/M	LN, supracl.	HV-CD#	+	-	-	History of thymoma (B1) 4 yrs ago, new LN enlargement, SSA+
10	17/F	Tonsil	HV-CD	+	-	-	Asymmetrically enlarged tonsil
11	47/F	LN, mesenteric	HV-CD	-	-	NA	Mesenteric mass
12	6/M	Soft tissue, arm	HV-CD	-	NA	NA	L upper arm mass
13	51/F	LN, mediastinal	HV-CD	+	-	-	Mediastinal LN enlargement
14	41/M	Gluteal mass	HV-CD	+	-	NA	Gluteal mass
15	32/F	LN, inguinal	HV-CD	+	-	-	Inguinal LN for 3 years

Abbreviations:

* , no systemic symptoms, unless otherwise shown.

, this case had intermediate features with increased plasma cells between atretic follicles; HV-CD, Castleman disease, hyaline vascular variant; PC-CD, Castleman disease, plasma cell variant; LN, lymph node; supracl, supraclavicular;