Indian J Hematol Blood Transfus (July-Sept 2019) 35(3):557–560
https://doi.org/10.1007/s12288-019-01096-8

CORRESPONDENCE

Anaplastic Diffuse Large B Cell Lymphoma: A Single Center Experience

Neha Singh[1] · Ridhi Sood[1] · Narendra Agrawal[2] · Sunil Pasricha[1] · Anurag Mehta[1]

Received: 12 October 2018 / Accepted: 7 February 2019 / Published online: 9 February 2019

Dear Sir,

The Anaplastic Diffuse Large B cell Lymphoma (A-DLBCL) is an uncommon distinct morphologic variant of DLBCL characterized by large polygonal cells with bizarre pleomorphic nuclei resembling tumor cells of anaplastic large cell lymphoma (ALCL) or even Reed-Sternberg cells of Hodgkin Lymphoma with a cohesive or sinusoidal growth pattern. A-DLBCL can also simulate malignant melanoma or undifferentiated carcinoma [1, 2]. It accounts for 1–3.5% of all newly diagnosed DLBCL cases according to different studies [3]. Diagnosis of A-DLBCL relies primarily on morphology and extensive immunohistochemical work-up in the absence of any single specific marker as the chances of false positive or erroneous diagnosis of A-DLBCL are higher due to close resemblance to other differentials such as ALCL, EBV-Positive DLBCL, ALK-Positive DLBCL and Hodgkin Lymphoma. Cases of A-DLBCL with hallmark cell appearance indistinguishable from common and giant cell-rich patterns of ALCL [4] and case reports of A-DLBCL with clear cells have also been described [5]. Because of its rarity, the clinico-pathologic characteristics of this entity have not been clearly defined. Previous case series and case reports have shown that clinical features and survival of patients with A-DLBCL are similar to DLBCL with centroblastic and immunoblastic morphology [6–12]. A single case report of follicular lymphoma transforming into anaplastic DLBCL of oral cavity has also been reported in Indian literature [13]. However, the largest multi-centric study on A-DLBCL patients published by Li et al. [8] which included thirty-five patients diagnosed, treated and followed over a 12-year period showed that A-DLBCL display characteristics distinct from conventional DLBCLs. Keeping these differences in mind, the present retrospective observational study was designed to evaluate the clinico-pathologic characteristics and prognostic outcome of patients diagnosed as A-DLBCL in our institution over a 8-year period from 2011 to 2018. We came across eleven cases of A-DLBCL out of 330 newly diagnosed cases of DLBCL (3.3%), which is similar to the incidence reported in literature. More importantly, the present study was one of the largest case series of A-DLBCL from a single institution in India.

Out of eleven patients of A-DLBCL, information regarding clinical characteristics and treatment details was available in nine patients as the remaining two cases came only for review of histopathological diagnosis. Their salient features have been summarized in Table 1.

Common symptoms at presentation were fever, weight loss, anorexia, weakness, cough, dyspnea, facial puffiness, hoarseness of voice etc. Median age of presentation was 63 years (range 19–77 years), with a female predilection (M: F ratio—4:7). Hypoalbuminemia (serum albumin < 3.5 mg/dl), elevated serum lactate dehydrogenase (LDH > 250 U/L) and anemia (Hb < 10 mg/dl) were observed in 6/9, 5/9 and 5/9 patients respectively. Mean hemoglobin of patients (g/dl) was 10.7 ± 2.94 while median serum LDH was 370.5 U/L (range 121–1085). All nine patients had Stage IV-B disease at presentation. IPI Scores $\geq$ 3/5 was observed in 77.7% (7/9) patients. However, bone marrow involvement was infrequent (22.2%). Infiltration of involved tissue by large pleomorphic atypical

✉ Neha Singh
drnehasingh123@gmail.com

[1] Department of Pathology and Lab Services, Rajiv Gandhi Cancer Institute and Research Center, Rohini, Delhi, India

[2] Department of Hemato-Oncology, Rajiv Gandhi Cancer Institute and Research Center, Rohini, Delhi, India

Table 1 Clinical and histomorphologic characteristics of A-DLBCL patients (n = 11)

CASE	Site of presentation	GC/N-GC Immuno phenotype	Extranodal sites involved	Degree of involvement by large bizarre cells;	CD30 expression	Ki-67 index	IPI-score (max score = 5)	Ann Arbor stage
1#	Axillary LN	N-GC	Spleen, bone marrow	Diffuse	Focal; Heterogenous	90–95	4	IV-B
2*	Sub-carinal LN	N-GC	Pleura, lungs	Focal	Strong	70–80	4	IV-B
3	Inguinal LN	GC	Bone, spleen	Diffuse	Strong	85–90	4	IV-B
4	Cervical LN	N-GC	Liver, spleen	Diffuse	Focal; Heterogenous	85–90	4	IV-B
5	Ileal Ulcer	GC	Liver	Diffuse	Focal; Heterogenous	50–60	2	IV-B
6	Anterior Mediatinal mass	N-GC	Pleura	Diffuse	Strong	50–60	3	IV-B
7#	Bone marrow	GC	Bone marrow	Focal	Focal; Heterogenous	30–40	2	IV-B
8	Pelvic bone	GC	Bone, soft-tissue	Diffuse	Strong	90	3	IV-B
9	Cervical LN	GC	Pleura, spleen	Diffuse	Strong	60–70	5	IV-B
10	Inguinal LN	GC	–	Diffuse	Focal; Heterogenous	60–70	–	–
11	Cervical LN	N-GC	–	Diffuse	Strong	60–70	–	–

Necrosis in Case 2 only

#Bone marrow involvement in Cases 1 and 7

LN lymph node, *GC* germinal center, *N-GC* non-germinal center

lymphoid cells was diffuse in majority of patients (9/11 = 81.8%) while only two had such atypical large cells scattered in a background of conventional DLBCLs (Fig. 1). Mitosis was significant with many atypical mitotic figures but necrosis was rare and focal. All eleven patients presented with de novo disease and were positive for CD20, LCA, CD30 and EMA with negative expression of ALK-1, CD3, EBER-ISH and CD15 henceforth ruling out other common differentials such as Hodgkin Lymphoma (lack of polymorphous background comprising of eosinophils, plasma cells, histiocytes etc. and absence of expression of CD15 and EBER-ISH), EBV- positive DLBCL, ALCL(lack of predominant sinusoidal pattern apart from classical IHC features) and ALK- positive DLBCL. Six (54.5%) patients had Germinal-Center like immunophenotype while remaining five (45.5%) had Activated B Cell- like immunophenotype. Proliferative index varied from 30-95% with only 36.4% patients having Ki-index > 80%. CD30 was positive in all eleven patients but the intensity of expression varied from focal and weak to diffuse and strong. Positive expression of c-myc, bcl-2 and bcl-6 on IHC was observed in 18.2%, 54.5% and 45.4% patients respectively. However, only one patient showed double expressor immunophenotype. Also, none of the eleven patients showed c-myc rearrangements by FISH using Zytolite break-apart probes.

All nine patients were started on R-CHOP regimen comprising of Rituximab 375 mg/m^2 intravenous, Cyclophosphamide 750 mg/m^2 intravenous, Doxorubicin 50 mg/m^2 intravenous, Vincristine 1.4 mg/m^2 intravenous and Prednisolone 100 mg orally once daily for 5 days per cycle. Response assessment was done by PET-Scan after four cycles of chemotherapy. Complete remission was achieved in four patients; partial remission in one and two patients had persistent disease while the remaining two patients were lost to follow up. Follow up in treated patients ranged from 6 to 21 months.

Few important points that were highlighted by the present study include:

Firstly, A-DLBCL patients were associated with anemia, elevated LDH levels, hypoalbuminemia, B symptoms, Stage IV disease and higher IPI scores. However, there was no predilection for male sex, non-germinal centre immunophenotype or abnormalities involving double hit molecular rearrangements. Some of the observations were similar to that of Li et al. [8] who showed that A-DLBCL patients have a higher IPI score ($\geq$ 3/5), elevated serum lactate dehydrogenase levels with more frequent

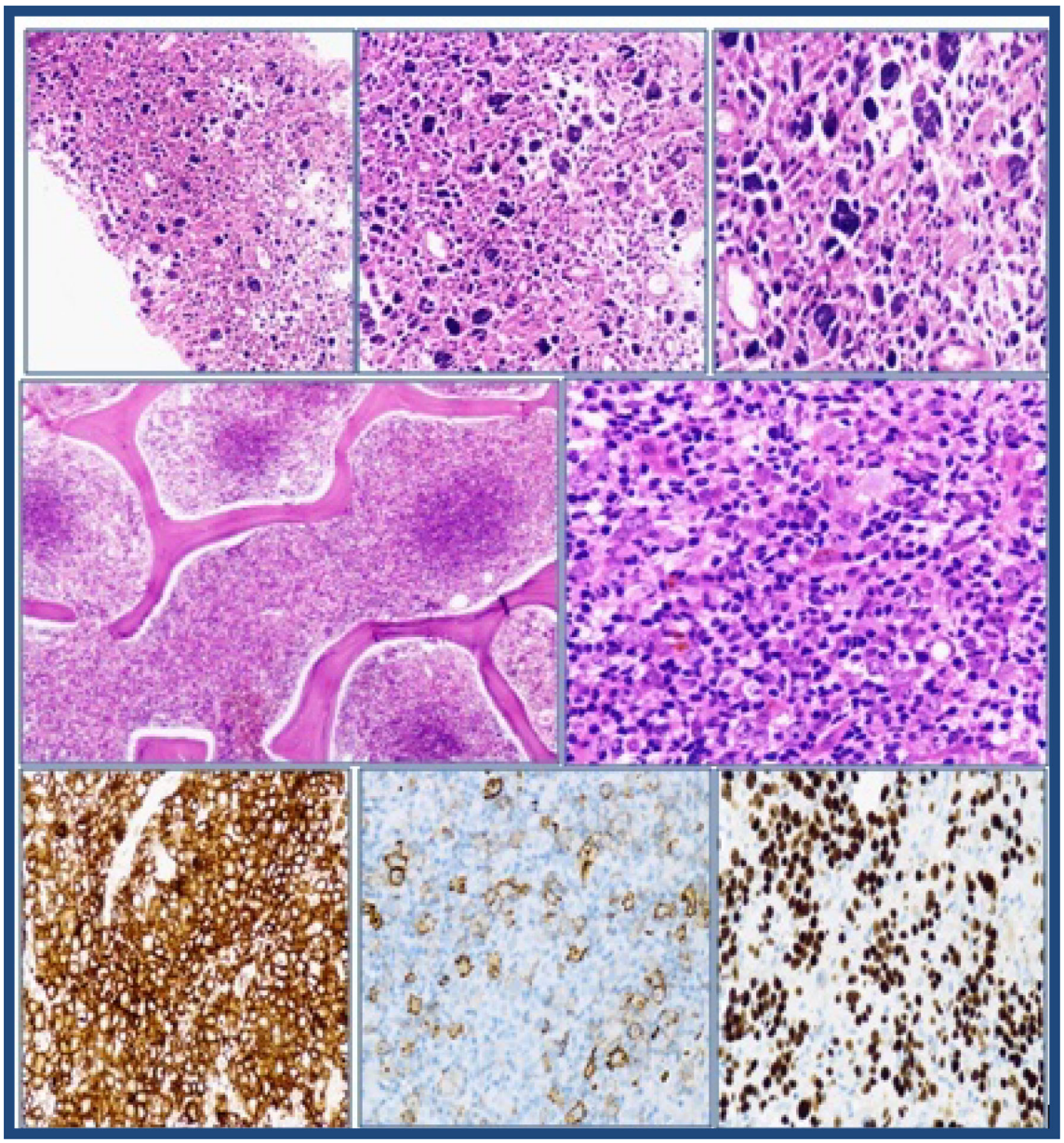

Fig. 1 First row shows low power and high power microphotographs with diffuse infiltration of involved tissue by large pleomorphic atypical lymphoid cells. Second row shows bone marrow involvement by few atypical large cells scattered in a background of conventional DLBCLs. Third row shows diffuse positive CD30, focally positive CD30 and variable Ki-67 proliferative index respectively

expression of CD30. However, unlike the present study, they found a strong association of anaplastic DLBCL with non-germinal center immunophenotype and concurrent genetic abnormalities of c-myc and/or bcl-6 and bcl-2. This brings us to the impression that the molecular profile of Indian A-DLBCL patients is considerably different from that of the West and more studies involving gene expression profiling or next generation sequencing are required to understand their pathobiology for optimal medical intervention.

Secondly, CD30, a member of TNFR superfamily is expressed in Hodgkins lymphoma, ALCL, PTCL-NOS, primary mediatinal large-B cell lymphoma and EBV-driven clonal lymphoproliferative disorders apart from 10 to 15% cases of DLBCLs [1]. Amongst the DLBCL cases, its expression is more frequently observed in the anaplastic variant. Few recently published studies evaluated the prognostic significance of CD30 expression in DLBCL patients and showed contrasting results. Hu et al. and Slack et al. reported that CD30 positive DLBCLs have superior 5-year Overall Survival and Progression-free survival in

both GC as well as N-GC subtypes [14, 15] while Hao et al. and Collie et al. observed that CD30 expression correlated well with B symptoms, bone marrow involvement, non-germinal center immunophenotype and poorer overall survival [16, 17], indicating a possible role of FDA approved Brentuximab vedotin, a CD30-directed antibody–drug conjugate in high-risk CD30-positive DLBCL patients. Brentuximab was not used in any of the A-DLBCL patients in the present study. Li et al. who associated A-DLBCL with less frequent CR to chemotherapy and a clinically aggressive behavior also showed their results in response to conventional chemotherapy such as R-CHOP or R-EPOCH [8]. It would be interesting to find out the therapeutic impact of Brentuximab vedotin in A-DLBCL patients in further studies in Indian settings.

Compliance with Ethical Standards

Conflict of interest The authors state that there is no conflict of interest present.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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