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Plasmablastic Lymphoma: Histopathological Features and Differential Diagnosis

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Abstract: ***Plasmablastic lymphoma (PBL) is a diffuse large B cell lymphoma with plasmacytic differentiation included in the WHO classification. Awareness of this entity and the availability of diagnostic markers have resulted in a recent increase in the number of PBL cases reported. A better understanding of tumour biology has widened the scope of developing new therapeutics, necessitating an accurate diagnosis of PBL. A 10 - year retrospective study was conducted in a regional cancer hospital, and cases diagnosed as PBL were retrieved. The results were categorised as HIV - positive, immuno - competent and pediatric patients. The clinical & biological parameters with morphology and immunohistochemistry (IHC) were analysed. Varied clinical presentations and morphological patterns were observed in PBL, resulting in various differentials, namely, carcinomas, round cell tumours, sarcoma, melanoma, high - grade lymphomas and anaplastic myeloma. The current study elaborates on the morphological features in core biopsies and IHC markers which aided the diagnosis of PBL. Varied morphological presentations differing from classical descriptions demand correlation with clinical and radiological parameters for including plasmacytic differentiation markers in providing an accurate diagnosis and deserved patient care.***

Keywords: plasmablastic lymphoma, morphology, differential diagnosis, immuno histochemistry

1. Introduction

Plasmablastic lymphoma (PBL) is a rare large B - cell non - hodgkin's lymphoma characterised by the diffuse proliferation of large B - immunoblast with plasmacytic differentiation. Delecluse and colleagues 1977 initially described the entity in the oral cavity of human immunodeficiency virus (HIV) positive patients.1 Eleven years later, WHO classification recognised PBL as a rare variant of diffuse large B cell lymphoma (DLBCL), accounting for 2% of acquired immunodeficiency syndrome (AIDS) - related lymphomas.2 A great diversity in presentation has been observed since the original report, which includes case reports not only in post - transplant and other immunodeficiencies, [3] but also in immunocompetent patients.4 Rarity of the lesion and its aggressive nature amplified with diagnostic challenges, lack of consensus in treatment and a high relapse rate explains its uniqueness. This study aimed to collect PBL cases and analyse their presentations and features. In addition, a literature review of new theranostic markers and their significance is also emphasised.

2. Materials and Methods

Patients diagnosed with PBL in the past ten years, all slides were retrieved and reviewed. Clinical data, including age, sex, site, radiology, performance status, bone marrow biopsy, Ann Arbor staging and therapeutic approach, were recorded. Biological data, including haemogram, LDH levels, serum uric acid levels, total protein, albumin and globulin levels and HIV status, were obtained. International prognostic indicator (IPI) was calculated. The hematoxylin and eosin slides and immunohistochemistry slides were retrieved from pathology department archives and re - reviewed. Immunohistochemistry was performed using the Ventana machine.4um of paraffin sections were fixed on poly L - lysine coated slides. Following fixation, slides were subjected to deparaffinisation and endogenous enzyme blocking by 0.3% hydrogen peroxide. Heat - mediated antigen retrieval was performed and then treated with primary and secondary antibodies. DAB working solution was added, and slides were counterstained and examined. IHC panel varied for individual cases. The primary immunohistochemical markers CD20 (L26), CD79a (SP18), and CD30 (Baer - H2) [cutoff threshold 20%], CD38 (SP149), CD138 (MI15), MUM1 (SP114) and Ki67 (MIB1).

3. Results

Epidemiology

PBL was diagnosed in 46 cases. A broad age group (7 - 82 years) with a median age of 45 was observed. The male - female ratio is 2.5: 1, predominantly affecting males. Of the 46 total reported cases, 78% (36 patients) were HIV positive, which included three pediatric cases, and 22% (10 cases) were non - reactive for HIV [Table 1].

HIV - positive patients

In the cohort of 46 cases, a higher incidence was seen in immunocompromised cases (33). Early age (median age 42 years) of presentation, increased incidence in males (Male female ratio 2.8: 1) and predilection for oral cavity was observed in immunosuppressed patients. Rare presentation in kidney and bone was seen. Bone marrow involvement at the time of presentation was noted only in HIV - positive cases. Serum uric acid and LDH were elevated in most patients. In cases presented with high IPI, 75% of cases were immunocompromised.

HIV - non - reactive cases

PBL in non - reactive cases was predominantly seen in an elderly population with higher median age (57 years) and increased incidence in females (Male female ratio 1.5: 1). PBL in immunocompetent patients seems more heterogeneous in terms of site of involvement. The predilection for sites like GIT (20%) and nodes (20%) in addition to the oral cavity (30%) were observed. Rare sites

gluteal region, lung and bone were also noted. Similar to HIV reactive cases, serum uric acid and LDH were elevated. Low IPI at the presentation time was reported in 60% of cases.

PEDIATRIC - cases

The pediatric population affected by PBL was immunocompromised and reported only in the oral cavity. Elevated LDH levels were noted, and a high IPI index was observed in the pediatric population.

IMMUNOHISTOCHEMISTRY (IHC)

Plasma cell markers CD38 were expressed in 93% (43) and CD138 in 84% (39) cases. All the instances expressed either CD38 or CD138. Strong MIB 1 and MUM 1 expression was observed in 97% (45) and 95% (44) cases, respectively. B cell markers, CD 79a, were seen in 26% of patients with varied positivity from focal to strong expression. Weak expression of CD 20 (4%), CD10 (7%) and Bcl - 2 (one case) in immunoblasts was observed. PAX5 was negative in all lesions. T cell markers expressed were CD2 (2%), CD3 (2%) and CD5 (2%). CD 30 antibody was expressed in 6% of cases. Epithelial marker EMA (26%) and mesenchymal marker vimentin (9%) were positive in immunoblasts. ALK and BCL - 6 were not expressed in any of the lesions. Based on the presentation site, various other IHC markers like CD99, CK 7, CK 5/6, cyclin D1, S100, PLAP, HMB 45, Melan A, Desmin and PAX8 were performed, and all were negative [Table 2].

Treatment

The treatment delivered in PBL is extensive, varying from local control to radiotherapy with various chemotherapy combinations. CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) and CHOP - like therapy, infusional EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) along with radiotherapy wereprovided in the institution.

Table 1: Epidemiology and clinical, biochemical and radiological features

	Total	HIV +ve	HIV non reactive
No of cases	46	36	10
Age <50 years	30	27	3
Age >50 years	16	9	7
Median Age of onset	45	42	57
Male Female ratio	2.5: 1	2.8: 1	1.5: 1
Localization			
Nodal	11	9	2
Extra nodal	35	27	8
Oral cavity	17	14	3
Nose/ pharynx	3	3	-
GIT	5	3	2
Soft tissue	6	5	1
Skin	1	1	
Kidney	1	-	1
Lung	1	-	1
Bone	1	1	
Bone marrow involvement	7	7	-
Multiple lymph nodes	36	30	6
Raised LDH levels	22	16	6
International prognostic index			
High	24	20	4
Low	22	16	6

Table 2: Immunohistochemistry (IHC) findings

	All cases (N= 46) No of cases (% of cases)			HIV positive (N=36) No of cases (% of cases)	HIV negative (N=10) No of cases (% of cases)
	Total +ve.	Weak +ve	Strong +ve		
CD138	40 (86%)	1 (2%)	39 (84%)	32 (88%)	8 (80%)
CD38	43 (93%)	1 (2%)	42 (91%)	35 (97%)	8 (80%)
MIB 1	46 (100%)	1 (2%)	45 (98%)	36 (100%)	10 (100%)
MUM 1	45 (98%)	1 (2%)	44 (96%)	35 (97%)	10 (100%)
CD79a	12 (26%)	8 (17%)	4 (9%)	10 (28%)	2 (20%))
CD20	2 (4%)	2 (4%)	-	1 (3%)	1 (10%)
PAX 5	-				
CD30	3 (6%)	-	3 (6%)	3 (8%)	
CD10	3 (6%)	1 (2%)	2 (4%)	3 (8%)	
Bcl2	1 (2%)	1 (2%)		1 (3%)	
Bcl 6	-				
EMA	12 (26%)	11 (24%)	1 (2%)	6 (16%)	6 (60%)
Vimentin	4 (8%)	1 (2%)	3 (6%)	3 (8%)	1 (10%)
CD2	1 (2%)	1 (2%)	-	-	1 (10%)
CD3	1 (2%)	1 (2%)	-	1 3%)	
CD5	-				

4. Discussion

Epidemiology and presentation

In the cohort of 46 cases of PBL, presentations varied clinically and morphologically. HIV - positivesubjects constituted 78% of the affiliate, similar to findings observed by Morisco J et al. and others[5 - 7]. Increased incidence in males (85%) was observed in HIV - positive cases, in contrast to that in females (58%) recorded in HIV - negative cases[5, 9]. PBL, irrespective of the immune status, is commonly observed in extranodal sites such as the oral cavity (37%). However, the incidence in the oral cavity is higher in immunosuppressed cases (82%) compared to the immuno - competent patients, as observed in literature[5 - 9]. HIV - negativesubjects exhibited varied site presentations such as GIT and lymph nodes when compared to HIV - positive cases as observed by Castillo J et al.6Bone marrow involvement as an initial presentation of PBL was observed only in HIV - positive patients in the current study. However, Praveen et al. have stated that bone marrow involvement as an initial presentation of PBL can be observed in HIV - negative cases also[10].

The higher median age of presentation (57 years) was recorded in non - reactive cases, comprising 40% of subjects older than 60 years, suggesting that increased age correlated with senescence of immunity[8]. Development of PBL following a localised inflammatory process was observed in one case with a history of a recurrent gluteal abscess. Similar cases have been reported by Tchernonog, E. et al suggesting a chronic inflammatory aetiology in the development of PBL in immuno - competent patients[9]. The oral cavity is most commonly exposed to trauma and infections; site predilection for the oral cavity in PBL, irrespective of the immune status, also suggests the presence of chronic inflammatory aetiology in the development of PBL. Hence, the immune system changes due to increased

age or chronic infections can predispose to PBL in otherwise immuno - competent patients.

PBL in the pediatric population is rare and constituted a tiny population (6%) in the current study[9]. PBL was observed only in HIV - reactive cases in contrast to other studies where PBL was also expressed in HIV - negative cases in the pediatric population[9].

The presence of multiple lymph nodes in ultrasound and CT scan was the most common presentation observed in 78% of cases, irrespective of their immune status. Bone marrow studies performed following the diagnosis of PBL showed involvement only in HIV - positive patients in the current study; however, marrow involvement in PBL has been observed in HIV - negative patients[5, 10]. The peripheral blood picture of the involved marrow had normal platelet, total and differential count, with only anaemia as an abnormal finding. No significant difference in biological parameters such as LDH, albumin globulin ratio and serum uric acid levels were observed between HIV - positive, HIV non - reactive and pediatric cases.

Decrease in CD4 and CD8 levels and increased viral load have been associated with disease progression in various studies[11]. Even response to PBL with HAART therapy has been recorded[11,] suggesting a direct association between immune status and prognosis in PBL. In the current study, Immunosuppressed cases presented with high IPI (75%) at the time of presentation, indicating poor prognosis[7]. Whereas HIV - negative cases usually presented with low international prognostic index scores, as recorded by Castillo J. J et al.1[2]

Biology and pathogenesis

Naive B - cells gain exposure to antigens in the germinal centre and undergo affinity maturation and DNA class switching to increase antibody diversity[12]. However, a subset of naive B - cells is transformed into plasma cells through a stochastic mechanism without antigenic stimulation[12, 14]. Plasmablasts are usually obtained in the transient process, during the conversion of centrocytes to plasma cells. These plasmablasts express CD138 and MUM1 & lose CD20 while still maintaining CD19 expression[12]. Plasmablasts are usually increased in reactive processes associated with a viral infection like EBV, HIV etc.

The proposed Pathogenesis of PBL is unclear, but the literature review states that the presence of MYC gene translocation along with EBV infection prevents apoptosis of activated B - cells, aiding the proliferation of plasmablasts [13, 15 - 18]. A recently analysed mutation in PRDM1 encodes BLIMP1 and alters the regulation of targets, including MYC[15].

Morphology

PBL is morphologically characterised by high - grade immunoblasts in sheets with focal plasmacytoid morphology. In the current study, PBL in the oral cavity showed predominantly monomorphic cells in sheets with occasional plasmablastic differentiation (fig 1) compared to other extra - nodal and nodal sites, where plasmablastic differentiation was evident (fig 1) [16]. Plasmablasts resemble large cells with a round eccentric nucleus, vesicular chromatin, prominent nucleoli and scant to moderate basophilic cytoplasm (Fig1) with an occasional perinuclear hoff. The presence of plasmacytic differentiation (eccentric nucleus and abundant cytoplasm) in the background of large immunoblasts aids the diagnosis of PBL. Mitotic activity varied from slight to brisk. The difference in mitotic activity is observed in not only different tumours but also different parts of the same tumour. Similar findings were observed in apoptosis and necrosis (Fig 1). Rarely starry sky patterns, as observed in high - grade B - cell lymphomas, can be present.

Small core biopsies posed a diagnostic challenge, mimicking various other malignancies. The presence of plasmablasts and immunoblasts aids in the diagnosis of PBL. Morphological patterns such as solid sheets, nested patterns and alveolar patterns with dys - cohesive cells were observed (fig 2). In addition to the typical plasmablasts and immunoblasts described, small round cells, plump to spindle cells and epithelioid - like cells were noted. In two cases observed in the lung and upper alveolus, predominantly round cells were seen (fig 2) resembling malignant round cell tumours; extensive search revealed focal clusters of large cells with prominent nucleoli favouring a differential of lymphoma in the lung, while in upper alveolus only malignant round cells were seen and IHC aided the diagnosis. The presence of plump spindle cells was usually observed at the areas of infiltration, accompanied by immunoblasts and plasmablasts at other regions. Depending on the amount of stroma, the tumour cells are arranged in solid sheets, small nests and alveolar patterns with dys - cohesive cells (fig 2). Occasionally, the amount of stroma was abundant, leading to the wide separation of tumour cells, which resulted in a nested pattern resembling an epithelial malignancy. However, dyscohesive pattern, lack of pleomorphism, and eccentrically placed nuclei with prominent nucleoli, it is essential to use an ihc panel of plasma cell markers. Abundant vascular hyperplasia, with glassy eosinophilic material deposited in the vessel and perivascular areas resembling amyloid (fig2), intermingled with tumour cells, was also noted. Crush artefact was observed in many biopsy specimens, and usually, deeper sections revealed the presence of plasmablasts.

In contrast to characteristic lymphoma morphology, as documented in the literature, various other patterns were observed in tiny core biopsies in our study. Hence, any case presenting with a history of HIV status with multiple lymph nodes without characteristic morphology deeper sections are to be submitted and examined meticulously for immunoblast and plasmacytoid cells. In addition, the IHC panel provided in such cases should always include plasma cell markers.

PBL closely mimics various other high - grade B - cell lymphomas such as immuno - blastic diffuse large B - cell lymphoma (IB - DLBCL), ALK - positive DLBCL, DLBCL with acute, chronic inflammation (DLBCL ACI), large B cell lymphoma HHV - 8 positive (DLBCL HHV8) and Burkitt's lymphoma, which is composed of immunoblasts with a high cell turnover [2, 17, 18]. Plasmablastic myeloma/ anaplastic multiple myeloma usually presents in extranodal sites and is the most common differential for PBL.

Anaplastic myeloma is traditionally seen in HIV - negative patients with monoclonal paraproteinemia, elevated calcium and renal parameters and lytic bone lesions. Morphologically, the pleomorphism in plasmablasts (multi - nucleation, hyper - lobation of nuclei) observed in anaplastic multiple myeloma is always absent in PBL[19]. Plasmablastic micro lymphoma arising from multicentric Castleman disease, a background of Castleman disease, usually distinguishes this entity from PBL[20].

IMMUNOHISTOCHEMISTRY (IHC)

I) Diagnostic markers: IHC is essential for diagnostic confirmation of PBL. CO - expression of B - cell (CD19, CD10, CD79a) and plasma cell markers (CD38, CD138) in large immature cells is a characteristic trait of PBL. Expression of B - cell and plasma cell markers supports the aetiology that tumour cells arise from the terminally differentiated post - germinal centre B - cells before transformation to plasma cells[12]. The plasmablastic cells are characterised by the expression of transcription factors associated with plasmacytic differentiation, CD38, CD138, Multiple myeloma 1 (MUM1), Blimp1, and XBP1, with decreased expression of CD20 and PAX5[21]. MIB - 1 index was more than 80% in all but one case confirming its high - grade aggressive nature. EBER is usually expressed, and LMP1 is rarely expressed in PBL[6, 9]. T cell markers CD2, CD3 & CD 5 aredescribed in rare cases. EMA expression was observed predominantly in HIV - negative cases (60%) compared to HIV - positive cases (16%) in the current study. Expression of EMA and vimentin in PBL can lead to misdiagnosis of carcinoma and sarcomas in core biopsies, further emphasising the inclusion of CD38 and CD138 markers in the IHC panel.

II) Differentiating markers: *CD 38 and CD138 strong expression is sensitive and specific for PBL. CD 38 and CD138 can also be expressed in DLBCL NOS and ALK - positive DLBCL.* However, the presence of all three B - cell markers CD20, CD79a and PAX - 5 favours the diagnosis of DLBCL, NOS (not otherwise specified), and the presence of ALK is essential for the diagnosis of ALK - positive DLBCL with plasmacytoid differentiation which also lacks CD20 and PAX 5 expression[22]. Primary effusion lymphoma also expresses EBV latency as expressed in PBL but lacks plasma cell markers and expresses HHV - 8[22, 23]. Plasmablastic myeloma expresses the B - cell and plasma cell markers as observed in PBL but lacks the expression of EBV. In rare cases differentiating PBL from plasmablastic myeloma may be extremely difficult, requiring molecular studies[23]. Plasmablastic micro lymphoma in the setting of MCD has an IgA and IgG light chain restriction and a strong association with HHV - 8[20].

III) Potential Therapeutic markers: MYC translocation has been observed in 50% of cases, and over - expression of MYC can be detected by IHC[5, 24]. Immunostains for programme death ligand - 1 (PDL - 1) showed moderate expression in microenvironment cells (60 - 72%) and tumour cells (22.5%) [25]. CD30 antibody expression was expressed in 6% of cases in the current study, and *Pretscher Det al.* state that targeted anti - CD30 antibodies can be tried in such cases[26]. Theranostic marker CD38, strongly expressed in PBL, can be an optimal target for anti - CD38 therapy.

Therapeutic advances in PBL

In PBL, the treatment delivered has been extensive, varying from local control with radiotherapy toa variety of chemotherapy combinations. The most common treatments include CHOP, CHOP - like therapy and infusional EPOCH. Several studies have experimented beyond standard chemotherapy. Other modalities like proteasome inhibitor (bortezomib), immunomodulatory agent (lenalidomide), anti - CD30 (brentuximab vedotin), and anti - IL6 &IL - 6 R antibodies were experimented[27]. These drugs were tried in short series, and multiple studies are required to confirm their efficacy.

5. Limitations

Paediatric cases constituted a small population in the current study. EBV, EBERish, a diagnostic and potential prognostic marker, was not performed in the present study. Studies regarding morphological analysis in PBL are not available due to the rarity of the lesion, necessitating further studies in assessing morphological patterns and their correlation with prognosis. Follow - up was not available; hence prognostic correlation was not performed.

6. Conclusion

The study illustrates that PBL has moved beyond the spectrum of HIV - positive cases. Considering clinical presentation and biological parameters at the time of presentation, prolonged immunosuppression over profound immunosuppression in the disease development seems likely. Various morphological patterns observed in PBL in core biopsy specimens are elucidated in the current study to avoid misclassifying these rare lymphomas, which have an advancing role in targeted therapies. Varied morphological presentations differing from classical lymphomas necessitate correlation with clinical and radiological parameters for inclusion of plasmablastic differentiation markers providing accurate diagnosis and deserved treatment.

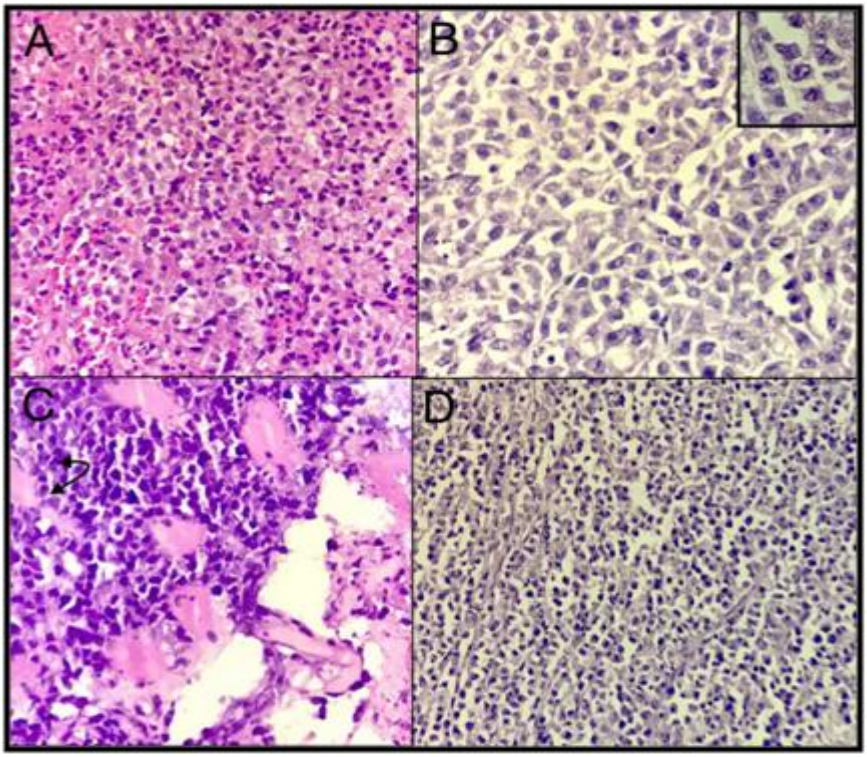

Figure 1: A) Sheets predominantly sheets of large immunoblasts intermingled with inflammatory cells. Plasmacytoid morphology is not evident. (40x). B) Sheets of large loosely arranged immunoblasts with prominent nucleoli and plasmacytic differentiation (40x). C) Tumor seen infiltrating the muscle with areas of necrosis seen on right side. Abundant mitosis noted (black arrow). (40x) D) Abundant apoptotic bodies seen ad mixed with tumor cells. (40x)

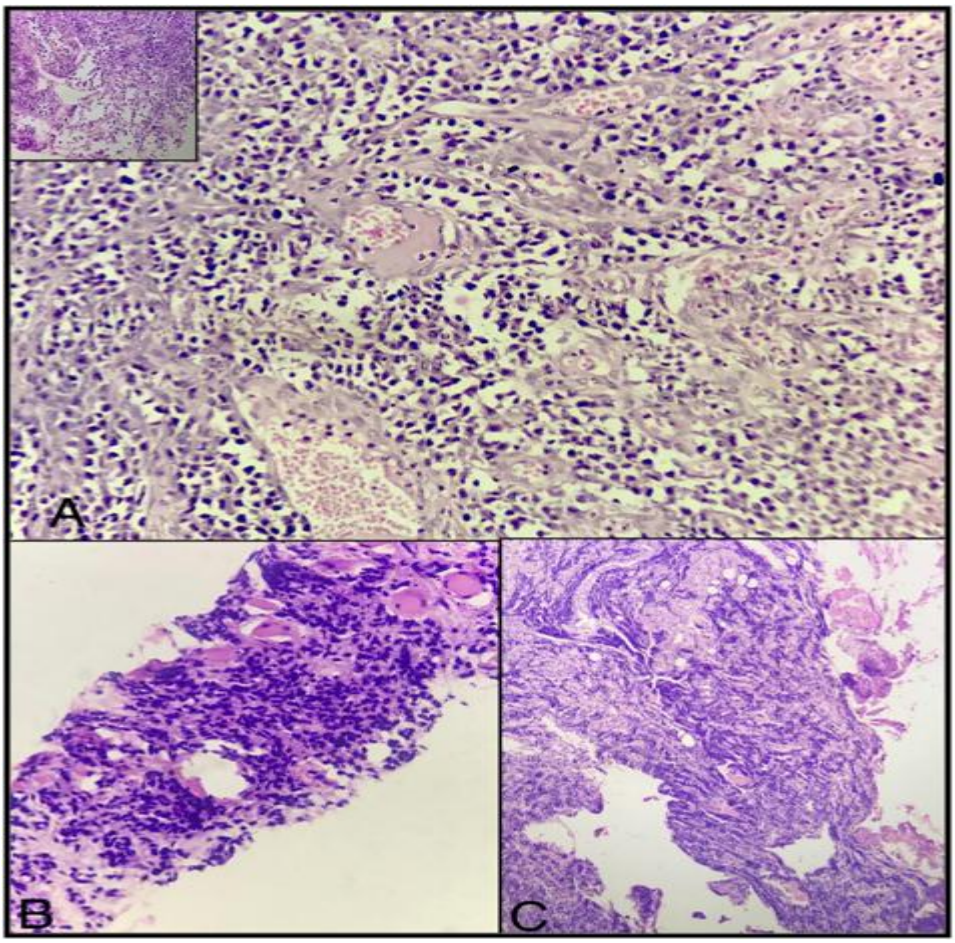

Figure 2: A) Dyscohesive cells with abundant vascular proliferation B) cells resembling malignant small round cell tumor and infiltrating the muscle C) Azzopardi effect noted in tumor cells. (20x)

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