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Pleural effusion as first sign of gray zone lymphoma: A case report

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Abstract

Background: Gray zone lymphoma (GZL) is a rare hematologic malignancy with overlapping features of diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL). It typically involves the mediastinum and shows variable clinical behavior, complicating diagnosis and management. While mediastinal masses are common, pleural effusion as the initial presentation is extremely rare. We report an exceptional case of GZL presenting primarily with pleural effusion, outlining the diagnostic and therapeutic challenges encountered.

Case presentation: A 41-year-old Arab woman with no notable medical history presented with progressive chest pain, dyspnea, night sweats, and weight loss over three months. Examination revealed signs of left-sided pleural effusion.

Results: Initial tests showed mild anemia and normal LDH. Chest X-ray confirmed a left pleural effusion. Pleural fluid was exudative with no malignant cells. Chest CT revealed a large anterior mediastinal mass with pleural thickening. Histopathological and immunohistochemical analysis of the biopsy identified a $CD30^+/CD20^+/CD15^-$ phenotype, confirming GZL. The patient underwent eight cycles of EPOCH-R chemotherapy, with full resolution of the effusion and complete metabolic remission on 18F-FDG PET/CT.

Conclusion: GZL requires a multimodal diagnostic approach including imaging, histopathology, and immunophenotyping. This case emphasizes the rarity of pleural effusion as an initial manifestation and the importance of early recognition to guide effective treatment. The favorable response to EPOCH-R supports its use as an accessible option in resource-limited settings, while underlining the need for heightened awareness of atypical presentations.

Keywords: Lymphoma; B-Lymphocytes; Pleural effusion; Immunohistochemistry; Antineoplastic combined chemotherapy Protocols; Hematological neoplasms.

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Introduction

Gray zone lymphoma (GZL) is a rare malignancy exhibiting overlapping morphological, immunophenotypic, and molecular features of diffuse large B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL) [1]. In the 5th edition of the World Health Organization (WHO) classification of lymphoid neoplasms (2022), GZL was formally recognized as a distinct entity, emphasizing the need to integrate clinical, histopathological, immunophenotypic, and genetic data for accurate diagnosis [2]. GZL most often arises in the mediastinum (mediastinal GZL, MGZL) but can also present in peripheral lymph nodes (non mediastinal GZL, NMGZL) [3]. MGZL shares epidemiological and clinical features with cHL—particularly affecting young adults in their 20s and 30s—but behaves more aggressively than both cHL and primary mediastinal B cell lymphoma (PMBCL), with poorer outcomes [4]. Because of its rarity and lack of standardized guidelines, treatment regimens for GZL are frequently extrapolated from those used for cHL or PMBCL, reflecting its intermediate biological profile [5]. We herein report a unique case of MGZL presenting initially with bilateral pleural effusion, and discuss diagnostic challenges and management in a resource limited setting.

Case presentation

Initial visit: A 41 year old Arabic woman with no significant hematological or oncological history presented to the emergency department with a 4 week history of progressive chest pain and dyspnea, accompanied by night sweats, unintentional weight loss over three months, persistent dry cough, and intermittent fever.

Clinical examination: On admission, she appeared in poor general condition with moderate respiratory distress. Vital signs were notable for fever (38.6°C), tachycardia (127 bpm), and oxygen saturation of 94% on room air. Chest auscultation revealed dullness to percussion and decreased breath sounds at the left lung base and reduced left hemithorax expansion.

Laboratory and radiographic findings: Initial blood tests demonstrated macrocytic anemia (hemoglobin 10.4 g/dL; normal 12-18 g/dL; mean corpuscular volume 113 fL; normal 80-100 fL), normal leukocyte count (8.07 × 10^9/L), and normal platelet count (397 × 10^9/L). Reticulocyte count was low (43 × 10^3/µL), creatinine and liver enzymes were within or near normal limits, and lactate dehydrogenase (LDH) was 268 U/L (normal 120-300 U/L). Chest X ray revealed a left pleural effusion; thoracentesis yielded sterile, exudative fluid with neutrophilic predominance and negative cytology for malignant cells.

Cross sectional imaging: A contrast enhanced chest CT angiogram showed regression of the pleural effusion with adjacent parenchymal collapse, and identified a large left anterior mediastinal mass measuring 100 × 85 mm in axial section and 116 mm in craniocaudal height. Mass exhibited multifocal pleural thickening, mediastinal lymphadenopathy, and encasement of critical structures including the aortic arch, pulmonary artery trunk, left atrium, ventricles, pericardium, and left upper lobar bronchus—without evidence of cortical bone invasion. Additional findings included multifocal nodular pleural thickening adherent to adjacent ribs and vertebrae (T1–T4, T10–T12) with left foraminal extension at T11 and diaphragmatic involvement.

Histopathology and immunohistochemistry: Given to the strong suspicion of an underlying malignancy, a biopsy of the mediastinal mass was performed, revealing the following findings: Morphologically, the tumor cells are sparse, large, Reed-Sternberg-like, with nuclei and prominent nucleoli, showing some mitotic figures (Figure 1B). Some cells exhibit retracted cytoplasm, reminiscent of lacunar cells (Figure 1C). These cells are associated with a dense inflammatory infiltrate composed mainly of lymphocytes, with rare eosinophilic polymorphonuclear cells. In certain areas, there are extensive areas of necrosis with a suppurative appearance, surrounded by numerous histiocytes (Figure 1A). Immunohistochemical analysis showed the tumor cells to be positive for CD30 and CD20, and negative for CD15 (Figures 1D, 1E and 1F), consistent with a diagnosis of mediastinal gray zone lymphoma (GZL).

Staging workup: Bone marrow biopsy showed normocellular marrow without lymphomatous involvement. 18F FDG PET/CT revealed hypermetabolic activity in the bulky mediastinal mass, left pleural thickening, supradiaphragmatic and infradiaphragmatic lymph nodes, and focal osseous and vertebral lesions—raising suspicion of stage IV disease. Spinal MRI confirmed pleural extension into costovertebral and foraminal structures and signal abnormalities in the right pedicles of T9 and T11 without epidural invasion.

Pre therapeutic assessment and treatment: Echocardiography showed left ventricular ejection fraction of 65%. Viral serologies (HBV, HCV, HIV) and serum protein electrophoresis were negative/normal. The patient received low molecular weight heparin for thromboprophylaxis, followed by six cycles of dose adjusted EPOCH R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab). Interim evaluation by chest X ray showed resolution of the effusion.

Follow up and outcome: Post treatment clinical assessment and repeat 18F FDG PET/CT confirmed complete metabolic remission. The patient entered a surveillance program with regular clinical and imaging follow up.

Discussion

Diagnostic challenges: The rarity of this disease is well documented, with the largest series reported by Evans et al., who conducted a multicenter retrospective analysis of 112 GZL patients diagnosed and treated between 2001 and 2012 across 19 North American academic centers [6].

GZL is an uncommon lymphoma subtype characterized by mixed morphological and immunophenotypic features of DLBCL and cHL. Morphologically, neoplastic cells may appear centroblastic or immunoblastic, with occasional Reed–Sternberg or lacunar type cells set within a mixed inflammatory milieu [4]. Immunohistochemistry is critical: GZL may express B cell markers (CD20, PAX5, OCT2, BOB1) variably, alongside CD30 and occasionally CD15—reflecting its transitional biology [7]. Compared to PMBCL, GZL demonstrates more frequent CD15 positivity and lower CD20 expression, and tends to occur more often in males [4]. In our patient, the $CD20^+/CD30^+/CD15^-$ profile paralleled a cHL like pattern, underscoring the entity's diagnostic complexity.

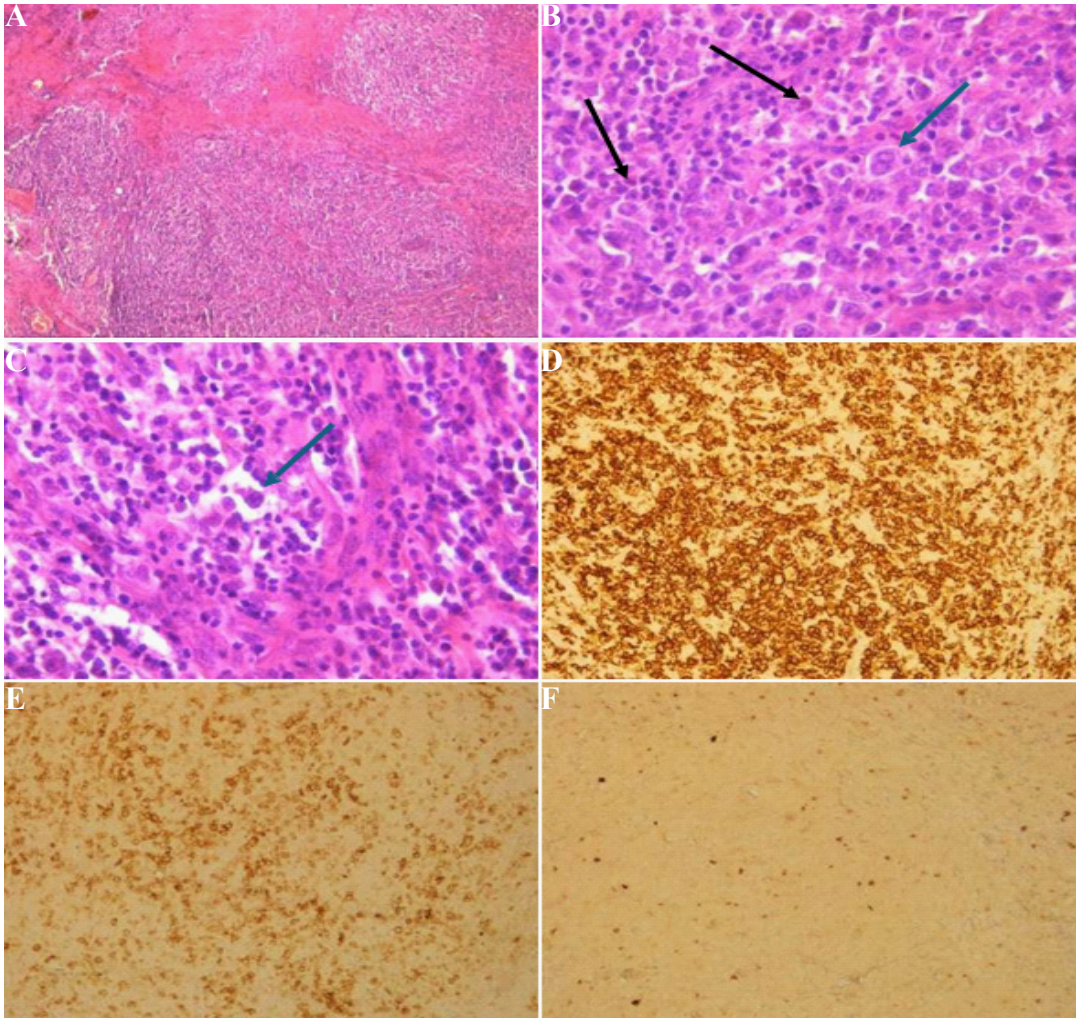

Figure 1: **(A)** Fibrosis with nodular growth proliferation reminiscent of nodular sclerosis classical Hodgkin's lymphoma (H&E staining, 40x). **(B)** The neoplastic cells are large, with oval to lobulated nuclei and conspicuous to prominent nucleoli with Reed–Sternberg-like cells (blue arrow), and numerous eosinophils (black arrow) (H&E staining, 400x). **(C)** Tumor cells resembling lacunar cells are present (arrow) (H&E staining, 400x). **(D)** Strong, homogeneous and diffuse CD20 positivity (immunostaining, 100x). The tumor cells are CD30 positive. **(E)** and CD15 negative. **(F)** (immunostaining, 100x).

Molecular features and limitations: Molecular data on GZL remain scarce due to its rarity. Reported chromosomal alterations include 9p24 locus gains/amplifications (encompassing PD L1/PD L2), 16p rearrangements, and 2p16 gains (REL locus) [8]. These findings suggest potential therapeutic targets (e.g., PD 1/PD L1 axis) but were unattainable in our setting given financial constraints—illustrating a common barrier in resource limited countries.

Therapeutic strategies: No consensus standard exists for GZL treatment. Intensive immunochemotherapy regimens, such as EPOCH R or BEACOPP, are frequently employed given the disease's aggressive nature. Emerging targeted therapies have shown promise: Santoro et al. reported significant anti tumor activity using brentuximab vedotin (anti CD30) plus nivolumab (anti PD 1) in a cohort of 10 MGZL patients [9]. However, high costs and limited availability restrict their use in low resource environments. In our case, EPOCH R was selected for its accessibility and documented efficacy.

Role of 18F FDG PET/CT: While data specifically addressing PET/CT in GZL are limited, its established utility in DLBCL and cHL supports its application in GZL for staging and response assessment. In our patient, baseline and post treatment PET/CT were instrumental in accurately staging the disease and confirming complete metabolic remission, respectively.

Conclusion

Mediastinal gray zone lymphoma (MGZL) is an uncommon and diagnostically complex malignancy. This case illustrates an exceptionally rare presentation with bilateral pleural effusion as the initial manifestation, emphasizing the need for heightened clinical suspicion. Accurate diagnosis relies on integrated clinical, histopathological, immunophenotypic, and imaging data. In resource-limited settings, accessible regimens like EPOCH-R offer effective management. Broader access to advanced diagnostics and therapies remains crucial to improving care.

Declarations

Acknowledgment : It is with great honor and appreciation that I take this opportunity to extend my deepest gratitude to the remarkable individuals comprising our Clinical Hematology Department team. In a setting where compassion meets expertise, their dedication and unwavering commitment shine brightly, illuminating the path to healing for our patients.

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To the entire team, from the diligent nurses and skilled technicians to the compassionate support staff and brilliant researchers, each one of them plays an indispensable role in our collective mission to provide exemplary care to those in need. Your dedication, professionalism, and unwavering commitment to our patients inspire us all and serve as a testament to the profound impact we can make when we work together toward a common goal.

Authors' contributions: AS and ZM analyzed and interpreted the patient data regarding the different presentations of the grey zone lymphoma. ZD, KM and ND focused on the management of this pathology in the literature. IB and SM examined the histopathological aspects and selected the most representative histological images to include in the manuscript. AS was a major contributor in writing the manuscript. SB and MAL supervised and validated this work. All authors read and approved the final manuscript.

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