RESEARCH PAPER

A Clinicopathological Spectrum of Rare and Aggressive Malignancies a Tertiary Care Centre: Highlighting Diagnostic Challenges and Multimodal Evaluation

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ABSTRACT

Background: Rare malignancies are diagnostically challenging due to heterogeneous morphology, overlapping features, and aggressive clinical behaviour. Tumors such as uterine carcinosarcoma, angiosarcoma, therapy-related acute monoblastic/monocytic leukaemia (t-AML M5B), mucinous ovarian carcinoma with signet-ring differentiation, and dedifferentiated liposarcoma often mimic more common conditions resulting in delayed diagnosis and poor prognosis.

Objective: To present five rare malignancies and emphasize the importance of integrated clinicopathological, immunohistochemical, and molecular evaluation.

Methods: A retrospective observational study of five histopathologically confirmed cases (November 2025 to April 2026) was conducted. We analyzed clinical, radiological, histopathological, immunohistochemical, and molecular findings. Tumors were classified according to the WHO criteria.

Results: The case series demonstrated diagnostic challenges including tumor heterogeneity, radiological misinterpretation, immunophenotypic overlap, and difficulty in distinguishing primary from metastatic disease.

Conclusion: A newer and multidisciplinary diagnostic approach is essential for accurate diagnosis of rare malignancies.

Keywords: Rare malignancy, Carcinosarcoma, angiosarcoma, Leukaemia, signet ring cell carcinoma, Liposarcoma

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INTRODUCTION

Rare malignancies represent a unique diagnostic challenge due to their low incidence and aggressive nature. Many of these tumors demonstrate overlapping morphological and immunohistochemical features with more common neoplasms often leading to misdiagnosis [2,3].

Recent advances in molecular pathology and updated classification systems, including the WHO and FIGO 2023 staging have improved diagnostic accuracy but require integration with clinical and radiological findings [1,5]. This case series highlights five rare malignancies and their diagnostic complexities.

Materials and methods

A retrospective observational study was conducted at a tertiary care centre during November 2025 to April 2026.

Inclusion Criteria:

- Histopathologically confirmed rare malignancies
- Complete diagnostic workup

Data Collection:

- Clinical and laboratory findings
- Radiological imaging
- Histopathology
- Immunohistochemistry
- Molecular/cytogenetic analysis

Tumors were classified according to the WHO classification systems [5].

Results:

Case 1: Uterine Carcinosarcoma with Heterologous Differentiation

A 69-year-old postmenopausal female presented with abnormal uterine bleeding. Imaging revealed a large heterogeneous endometrial mass. Haemoglobin: 9.6 g/dL – anaemia- microcytic hypochromic pattern, WBC: 35,340/cmm – marked leucocytosis, Neutrophils: 88% – neutrophilia, Platelets: 4.87 lakh/cmm – thrombocytosis. **Interpretation:** Progressive anaemia and marked inflammatory/leukemoid response over time, which is suggesting tumor burden or systemic stress.

Renal Function: Mild hyponatremia, Liver Function Test: ALT, AST, ALP, and GGT: Increased, Total Protein and Albumin: Decreased. **Interpretation:** Indicates hepatic dysfunction, possible tumor-related systemic effects, or metastatic/secondary involvement.

PT: Mildly prolonged, INR: 1.23 (slightly elevated) and APTT: within normal limits. **Interpretation:** Suggests mild coagulation disturbance.

Ultrasound of Abdomen and Pelvic: Approx. 9.5 × 6 cm heterogeneous mass involving uterine endometrium with mild increased vascularity and no calcification. Radiologically suggestive of a neoplastic lesion.

Histopathology demonstrated a biphasic tumor composed of malignant epithelial and mesenchymal components with rhabdomyoblastic differentiation. Uterine carcinosarcoma is a highly aggressive tumor characterized by dual differentiation and poor survival outcomes [1,6].

Immunohistochemistry (IHC) Findings and Interpretation: **CK, CK7, PAX8:** Focal positivity → epithelial differentiation consistent with carcinoma component. **CD10, Vimentin:** Patchy positivity → stromal/sarcomatous differentiation. **Desmin & Myogenin:** Focal positivity → skeletal muscle differentiation suggesting rhabdomyosarcomatous element. **P16:** Diffuse positivity → high-grade aggressive tumor. **Ki-67 (55–60%):** High proliferation index. **ER/PR:** Negative → hormone receptor negativity (aggressive behaviour). **P53:** Mutant null pattern → high-grade serous carcinoma association. **Cyclin D1 & H-Caldesmon:** Negative → excludes certain smooth muscle tumors like Leiomyoma, Leiomyosarcoma (malignant smooth muscle tumor and Smooth muscle tumors of uncertain malignant potential (STUMP)

Our final diagnosis is **Carcinosarcoma composed of high-grade serous carcinoma with endometrial stromal sarcoma and focal rhabdomyosarcoma components. [Figure 1]**

Case 2: Primary Splenic Epithelioid Angiosarcoma

A 47-year-old female presented with severe hepatosplenomegaly and anaemia. Radiology suggested benign vascular lesions. Haemoglobin: 7.5 g/dL – anaemia, microcytic hypochromic pattern, WBC: 10,470/cmm – marked leucocytosis, Platelets: 1.31 lakh/cmm – thrombocytopenia.

Interpretation:

Findings suggest persistent anaemia with progressive thrombocytopenia and leucocytosis, likely related to splenic pathology and tumor infiltration. Liver and Renal Function Tests: **Within normal limits**

Ultrasound Abdomen: Spleen enlarged, lobulated with heterogeneous echo pattern, multiple hepatic haemangiomas, multiple splenic haemangiomas, splenomegaly, and minimal ascites.

Contrast Enhanced CT Abdomen and Pelvis: Liver: Multiple well-defined hypo dense lesions, Peripheral nodular enhancement in arterial phase, Progressive centripetal fill-in in delayed phase. Features consistent with haemangiomas. **Spleen:** Enlarged spleen measuring 13 cm. Multiple hypo dense lesions with similar enhancement pattern. Radiologically suggestive of vascular tumors/haemangiomas

Histopathology revealed malignant vascular proliferation with epithelioid morphology. Angiosarcoma in spleen are rare, aggressive tumors that frequently demonstrate nonspecific clinical and radiological features, leading to misdiagnosis [2,3].

IHC showed positivity of CD34, ERG, and FLI-1, confirming endothelial differentiation.

Our final diagnosis was **Epithelioid angiosarcoma of spleen [Figure 1]**

Case 3: Therapy-Related Acute Monoblastic/Monocytic Leukaemia (t-AML M5b)

A 52-year-old female, a known case of breast carcinoma, presented with progressive fatigue, fever and easy bruising for 3 weeks. She had undergone a left sided modified radical mastectomy followed by anthracycline-based chemotherapy, topoisomerase II inhibitors, and radiotherapy one year prior. She was currently on hormonal therapy. There was no previous history of hematological disorders. Haemoglobin: 7.5 g/dL, Total Leukocyte Count: 28,600 /µL, Platelet Count: 42,000 /µL

Peripheral Blood Smear: Microcytic hypochromic anaemia, marked leucocytosis with circulating blasts (~60%), Blasts: 48% and Promonocytes: 12% (Large blasts with basophilic cytoplasm, folded nuclei, fine granulations and cytoplasmic vacuolation.

Morphology suggestive of monocytic lineage. Thrombocytopenia present. Elevated LDH indicate high cell turnover and mildly elevated uric acid

Bone marrow examination revealed monocytic blasts. First, we do Flow cytometry but it shows negative for all monocytic and myelocytic markers due to therapy related antigen loss or phenotyping alteration. Cytogenetic analysis showed 11q23 rearrangement, a hallmark of therapy-related leukaemia associated with poor prognosis [4].

Our final diagnosis was basis on Molecular findings supportive of therapy-related Acute Monoblastic/Monocytic Leukaemia (M5b) **[Figure 2]**

Case 4: Ovarian Mucinous Carcinoma with Signet-Ring Differentiation

A 51-year-old female presented with ascites and abdominal distension. Cytology revealed Positive for malignant cells — features suggestive of mucin-secreting adenocarcinoma, likely ovarian in origin.

Haemoglobin: 9.6 g/dL – anaemia, microcytic hypochromic pattern, WBC: 18,845/cmm – marked leucocytosis, Neutrophils: 85% – neutrophilia, Platelets: 4.87 lakh/cmm – thrombocytosis. **Interpretation:** Progressive anaemia and marked inflammatory/leukemoid response over time, suggesting systemic stress.

Liver Function Test: ALT, AST, ALP and GGT: Increased, Total Protein and Albumin: Decreased. **Interpretation:** Indicates hepatic dysfunction, possible ascitic effusion-related systemic effects or metastatic/secondary involvement.

Differentiating primary ovarian tumors from metastatic gastrointestinal malignancies is a major diagnostic challenge, particularly in signet-ring morphology [7]. After exclusion of metastasis from GIT, a diagnosis of **mucinous ovarian malignancy with malignant ascites** was made. Final diagnosis was **Mucinous cystadenocarcinoma of the ovary with signet-ring cell differentiation. [Figure 3]**

Case 5: Dedifferentiated Liposarcoma with Angiosarcomatous Differentiation

A 52-year-old female presented with a retroperitoneal mass. Haemoglobin: 8.2 g/dL – anaemia, microcytic hypochromic pattern, WBC: 8200/cmm, MCV: 59fl, Platelets: 4.73 lakh/cmm – thrombocytosis, ESR: 60mm/hr. **Interpretation:** Microcytic hypochromic anaemia with reactive thrombocytosis and elevated ESR suggest chronic inflammatory or malignant process.

Ultrasonography (USG): Suspicious for malignant ovarian neoplasm with peritoneal spread.

MSCT Abdomen and Pelvis: More likely Retroperitoneal liposarcoma.

Histopathology showed well-differentiated liposarcoma transitioning into high-grade sarcoma with angiosarcomatous differentiation. Dedifferentiated liposarcoma is characterized by MDM2/CDK4 amplification and aggressive clinical behaviour [8].

Our final diagnosis was **Dedifferentiated Liposarcoma with Focal Myxoid Change and Heterologous Angiosarcomatous Differentiation. (mpT4 AJCC 8th Edition) [Figure 3]**

Discussion:

This case series highlights several important diagnostic challenges:

- **Tumor Heterogeneity in the case of** Carcinosarcoma and liposarcoma demonstrates divergent differentiation, complicating diagnosis [1,8]. This case represents a high-grade triphasic malignant uterine tumor presenting as postmenopausal bleeding. Progressive anaemia, marked leucocytosis, thrombocytosis, and deranged liver enzymes reflected systemic tumor effects. Radiology demonstrated a large vascular endometrial mass. Histopathology suggested a high-grade malignant neoplasm with mixed epithelial and mesenchymal differentiation, which was definitively confirmed by immunohistochemistry as carcinosarcoma with heterologous rhabdomyosarcomatous differentiation. The absence of ER/PR and high Ki-67 index indicates aggressive biological behaviour.
- **Radiological Mimicry-** Angiosarcoma may resemble benign vascular lesions, leading to delayed diagnosis [2]. Primary splenic epithelioid angiosarcoma is an extremely rare and highly aggressive vascular malignancy that often mimics benign vascular tumors such as haemangiomas on imaging, leading to diagnostic delay. The presence of severe anaemia, progressive thrombocytopenia, and splenomegaly should raise suspicion for malignant splenic pathology despite benign radiological impressions. Histopathology with confirmatory endothelial immunomarkers remains the gold standard for diagnosis. Early recognition is critical due to the tumour's aggressive behaviour, risk of spontaneous rupture, haematogenous spread, and poor prognosis. This case highlights the importance of integrating clinical, radiological, histomorphological, and immunohistochemical findings to achieve accurate and timely diagnosis [2].
- **Diagnostic Discordance in the case of therapy-**related Acute Monoblastic/Monocytic Leukemia (M5B) often requires cytogenetic confirmation due to inconclusive morphology or flow cytometry [4]. This case highlights therapy-related AML as a serious late complication following exposure to anthracyclines and topoisomerase II inhibitors. The presence of 11q23 rearrangement strongly supports therapy-related leukemogenesis. Discordance between morphology and flow cytometry underscores the importance of integrated diagnosis using morphology, cytogenetics, and molecular testing. Early recognition is critical due to the aggressive clinical course and distinct therapeutic implications of therapy-related AML [4].
- **Primary vs Metastatic Dilemma -** Signet-ring morphology necessitates exclusion of metastatic disease, especially from gastrointestinal tract [7]. This case demonstrates a mucinous ovarian malignancy presenting with malignant ascites and signet-ring cell differentiation, a feature that may mimic metastatic gastrointestinal adenocarcinoma. Early cytological evaluation of ascitic fluid played a key role in raising suspicion for malignancy and guiding further radiological investigations. Radiological exclusion of a gastrointestinal primary supported the diagnosis of a primary ovarian tumor. The presence of invasive growth, necrosis, stromal desmoplasia, and signet-ring morphology indicates aggressive biological behavior, highlighting the importance of early detection, accurate pathological diagnosis, and prompt management [7].
- **Role of Molecular Diagnostics-** Recent classification systems emphasize molecular profiling for accurate diagnosis and prognosis [1,5]. Retroperitoneal liposarcoma can grow to massive size due to their silent anatomical location. This case

mimicked malignant ovarian neoplasm on ultrasonography, highlighting diagnostic challenges. Dedifferentiated liposarcoma with angiosarcomatous differentiation is rare and associated with aggressive behaviour. Multimodal imaging is essential for correct preoperative planning. Complete surgical excision remains the cornerstone of treatment. High-grade histology and heterologous differentiation suggest increased risk of recurrence and metastasis, warranting close follow-up. This case emphasizes the importance of radiologic-pathologic correlation in retroperitoneal masses. Massive dedifferentiated liposarcoma with heterologous angiosarcomatous differentiation is rare and may clinically simulate gynaecologic malignancy. Early diagnosis, meticulous surgical resection, and histopathological evaluation with immunohistochemistry are crucial for optimal management and prognostication [1,5].

Conclusion:

Rare malignancies require:

- High clinical suspicion
- Multidisciplinary evaluation
- Integration of morphology, IHC, and molecular diagnostics
- Awareness of rare entities

Early and accurate diagnosis is essential to improve patient outcomes.

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Figure with legends:

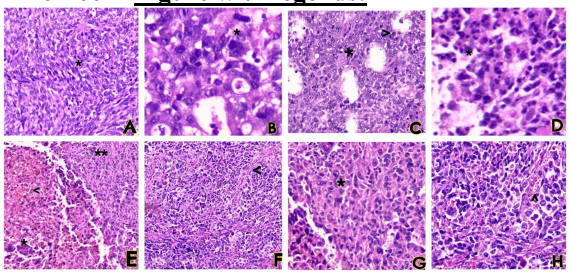
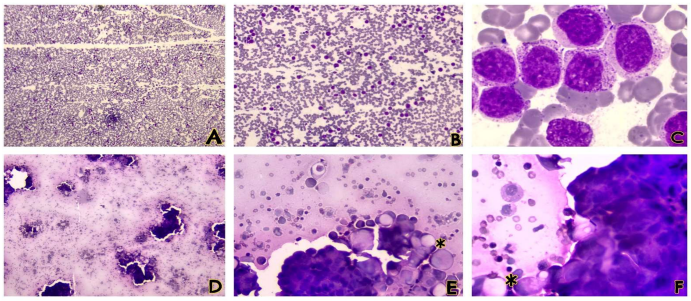


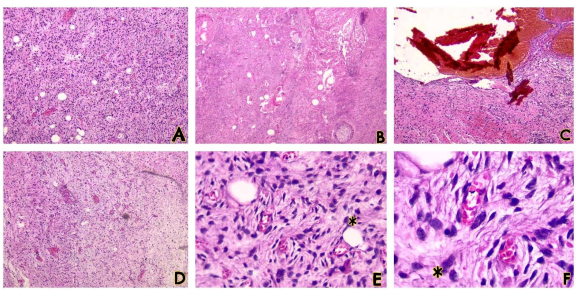
Figure: 1 Case 1: Uterine Carcinosarcoma with Heterologous Differentiation & Case 2: Primary Splenic Epithelioid Angiosarcoma; **A:** Malignant cells in fascicles of atypical spindle cells (*). (20X, H&E); **B:** Solid areas showing spindle cells arranged in fascicles within tightly packed vascular space, presence of eosinophilic hyaline globules in spindle cell cytoplasm (*) and



[Figure 3] Case 5: Dedifferentiated Liposarcoma with Angiosarcomatous Differentiation; A: Areas of well-differentiated a liposarcoma showing atypical adipocytes and lipoblasts with tumour cells re spindle-shaped cells arranged in a storiform pattern. The cells show marked cellular pleomorphism, with enlarged, irregular, hyperchromatic nuclei, coarse chromatin, and conspicuous nucleoli. Anastomosing vascular channels. (4X, H&E); **B:** Areas of well-differentiated liposarcoma showing atypical adipocytes and lipoblasts with tumour cells are spindle-shaped cells. Focal myxoid stromal change. (4X, H&E); **C:** Focal myxoid stromal change, Heterologous angiosarcomatous differentiation characterized by: Anastomosing vascular channels, Endothelial atypia and areas of haemorrhage, (4X, H&E); **D:** Focal myxoid stromal change, Heterologous angiosarcomatous differentiation characterized by: Anastomosing vascular channels, Endothelial atypia and areas of haemorrhage, (4X, H&E); **E:** Malignant cells show high nuclear-cytoplasmic ratio, marked pleomorphism, high mitotic activity and moderate nuclear and cytoplasmic atypia.(*) (20X, H&E); **F:** Tumour (spindle shaped) cells show marked cellular pleomorphism, with enlarged, irregular, hyperchromatic nuclei, coarse chromatin, and conspicuous nucleoli.(*) (40X, H&E)

hyalinization of blood vessels. (20X, H&E); **C:** Malignant cells (>) in trabecular (*) and glandular arrangement with high N:C ratio, pleomorphism, irregular nuclei, fascicles of atypical spindle cells. (4X, H&E); **D:** Round malignant cell component shows occasional rhabdoid cells with abundant eosinophilic cytoplasm (*) (10X, H&E); **E:** Malignant cells arranged in solid areas (**), papillary structures, glomerular pattern (*) and fragmented anastomosing vascular channels (<). Cell shows high nuclear-cytoplasmic ratio, marked pleomorphism, high mitotic activity and moderate nuclear and cytoplasmic atypia. (10X, H&E); **F, G, H:** Malignant cells show high nuclear-cytoplasmic ratio, marked pleomorphism, high mitotic activity (^) and moderate nuclear and cytoplasmic atypia. Solid areas showing spindle cells arranged in fascicles within tightly packed vascular space (*), presence of eosinophilic hyaline globules in spindle cell cytoplasm and hyalinization of blood vessels (<). (20X, H&E)

[Figure: 2] Case 3: Therapy-Related Acute Monoblastic/Monocytic Leukemia (t-AML M5b) & Case 4: Ovarian Mucinous Carcinoma with Signet-Ring Differentiation; A: Peripheral smear: Hypercellular (4X, Leishman stain)**; B:** Peripheral smear: Hypercellular with blasts constitute approximately 60–65% of nucleated cells. (10X, Leishman stain)**; C:** Peripheral smear: Blast cells constitute approximately 60–65% of nucleated cells, Predominance of monoblasts and promonocytes, Cells with folded nuclei, fine chromatin, and prominent nucleoli (100X, Leishman stain)**; D:** Highly cellular smears, numerous malignant epithelial cells in clusters, sheets, and singly scattered. (4X, MGG)**; E:** Cells showed: Abundant intracytoplasmic mucin, eccentrically placed nuclei with compressed chromatin, Prominent nucleoli. (*) (10X, H&E)**; F:** Cells showed: Abundant intracytoplasmic mucin, eccentrically placed nuclei with compressed chromatin, Prominent nucleoli. Presence of characteristic signet-ring cells (*). Background contained mucinous material and inflammatory cells (20X, MGG)



Highly cellular smears, numerous malignant epithelial cells in clusters, sheets, and singly scattered. (4X, MGG)