Invasive Ductal Carcinoma of Breast with Neuroendocrine Differentiation: A Case Report.

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Abstract

Primary invasive breast carcinoma with neuroendocrine differentiation is an uncommon presentation. We hereby report a case diagnosed as invasive ductal carcinoma with neuroendocrine differentiation in a 52-year-old female who presented with a painless right breast lump.

Introduction:

Invasive carcinoma with neuroendocrine features is a rare entity that accounts for 2-5% of all invasive carcinoma of the breast (1). It has comparable histological features with other neuroendocrine tumors of the gastrointestinal tract, pancreas, and bronchopulmonary system with different percentages of neuroendocrine markers. The diagnosis of the neuroendocrine tumors of the breast is specially done based on immunohistochemistry which is not routinely done for the tumors of the breast, so the exact incidence is still unknown (2). Some literature report that neuroendocrine tumors are seen in up to 30% of invasive carcinoma commonly associated with solid papillary carcinoma, invasive ductal carcinoma, and mucinous carcinoma of the breast (3). A novel hypothesis states that the tumor arises from differentiating neoplastic stem cells into epithelial and endocrine lines as a consequence of the unusual differentiating event during carcinogenesis (4). The neuroendocrine markers like chromogranin A or B and synaptophysins are generally positive for these cancers (5). Here, we present a case of a rare variant of the invasive ductal breast with neuroendocrine differentiation.

Case report:

A 52-year-old female presented with a painless right breast lump for one week. On local examination of the breast, the mass measured 6 cm x 4 cm and was located at 12 o'clock position. The overlying skin and nipple-areolar complex were unremarkable. Axillary lymph nodes were not palpable. Initially, the patient was evaluated with a mammogram which showed a lobulated dense mass measuring 49 mm x 48 mm situated in the upper inner quadrant of the right breast (BI-RADS category 4a). Further evaluation with fine-needle aspiration cytology (FNAC) was suggestive of ductal carcinoma. Computed tomography (CT) scan of the chest showed heterogeneously enhancing mass measuring 4.4 cm x 4.3 cm in the upper inner quadrant of the right breast with surrounding perilesional fat stranding and few right axillary lymph nodes with maintained fatty hilum but thick eccentric cortex-likely to be metastatic. (Figure 1)

A diagnosis of ductal carcinoma was made on histopathological evaluation of USG guided tru-cut biopsy. The patient underwent right breast mastectomy with frozen section examination of right axillary sentinel

lymph nodes. On frozen section examination, four lymph nodes identified were uninvolved by carcinoma. Gross examination revealed a unifocal tumor located in the upper inner quadrant with the greatest dimension of 4 cm. Histopathological examination revealed tumor cells arranged in diffuse sheets and pseudorosettes. These tumor cells have round to oval nuclei, powdery chromatin with scant cytoplasm. Mitosis and areas of necrosis were noted (Figure2). Further, immunohistochemistry showed tumor cells positive for cytokeratin (CK), focally positive for insulinoma-associated protein 1(INSM-1), cluster of differentiation 56 (CD56), and negative for transcription factor GATA3, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her2 Neu) with nuclear protein (Ki67) proliferation of about 40% (Fig. 3).

Based on cumulative information obtained from all the diagnostic procedures including histopathology and immunohistochemistry, the final diagnosis of invasive carcinoma with neuroendocrine differentiation was considered. The pathological stage was pT2 (sn) N0. The postoperative period was uneventful. The patient has received 4^{th}cycle of chemotherapy with Carboplatin and Docetaxel 3 weekly (L1C4 completed) to date. USG of breast, chest X-ray, USG of abdomen and pelvis, and the metabolic panel was performed at 4 months of follow up which showed no evidence of recurrence of the disease.

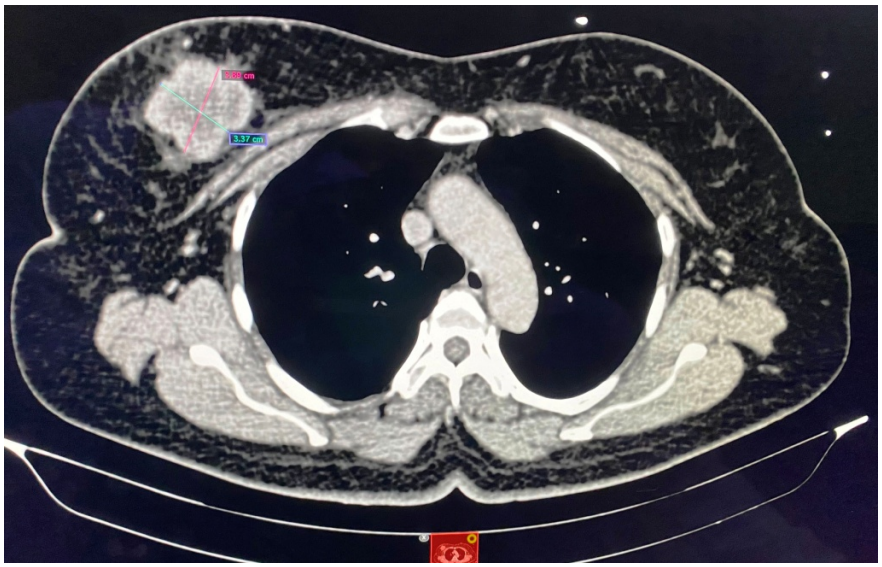
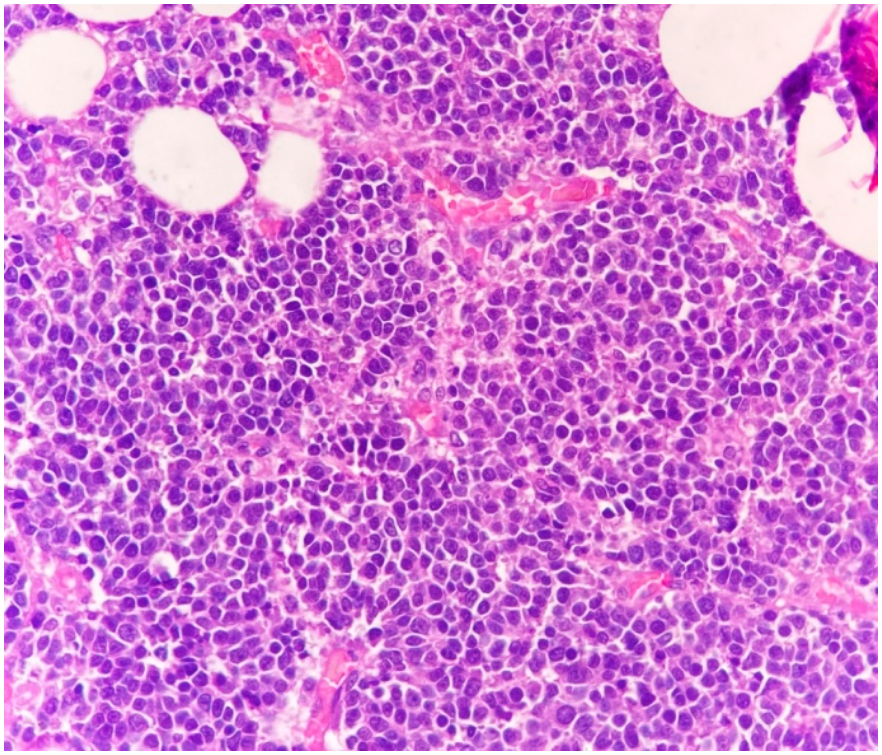
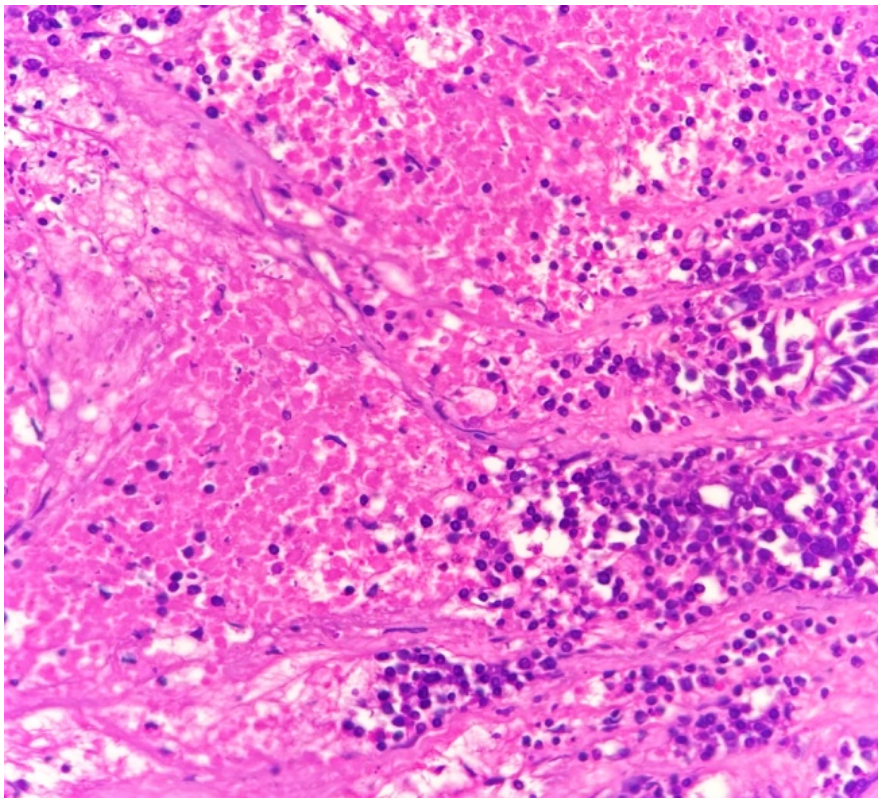


Figure 1: Computed tomography (CT) scan of the chest showing a large lobulated heterogeneously enhancing mass (white arrow).





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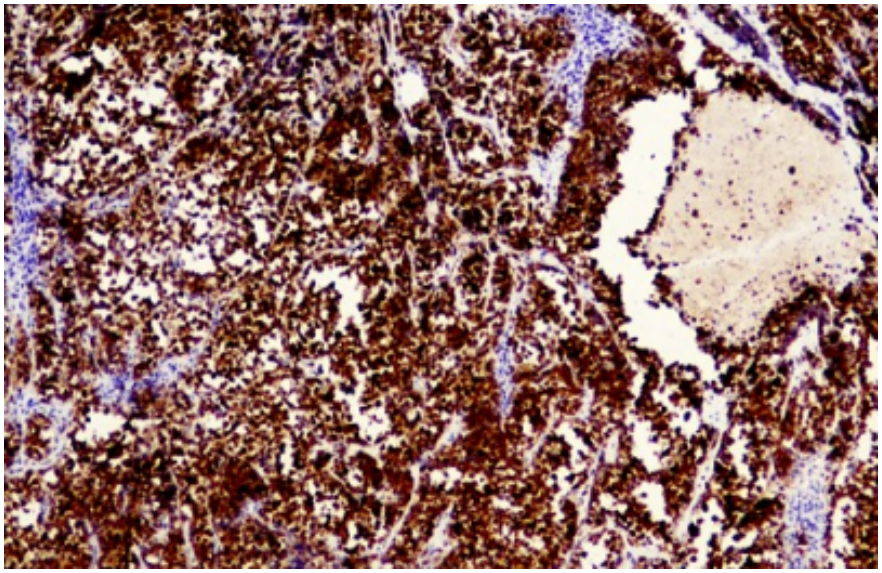
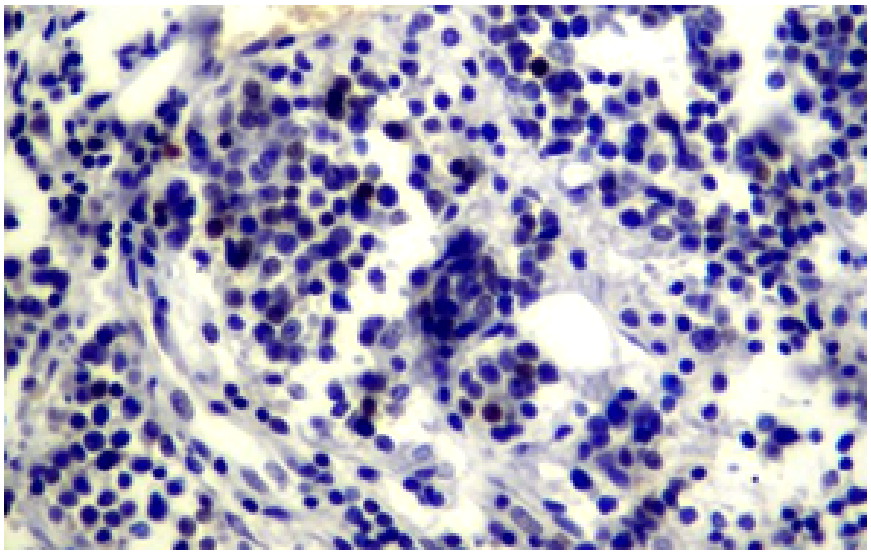
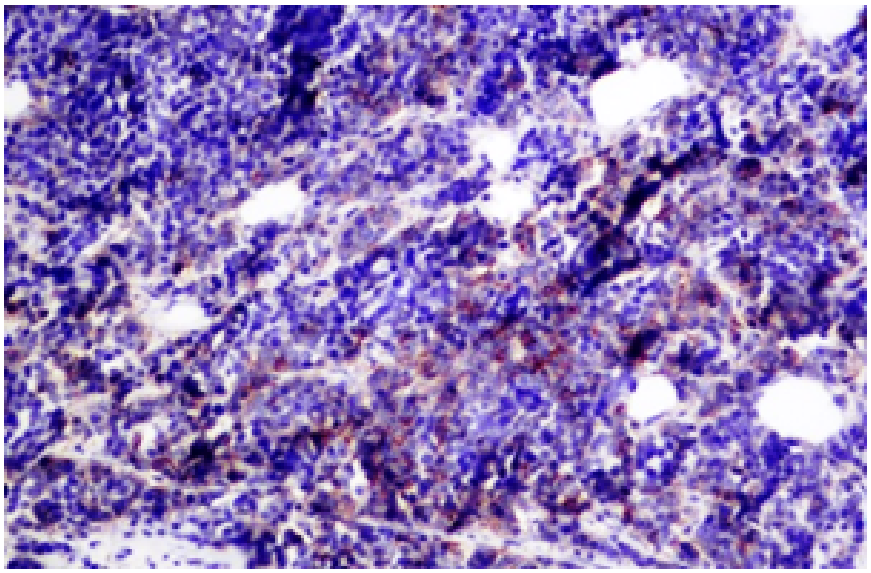
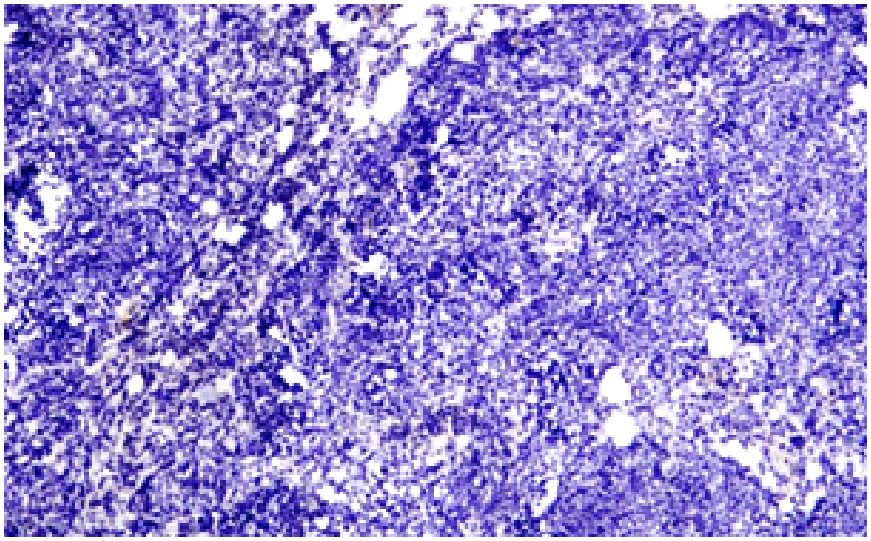
(B) Areas of necrosis and apoptotic bodies were noted









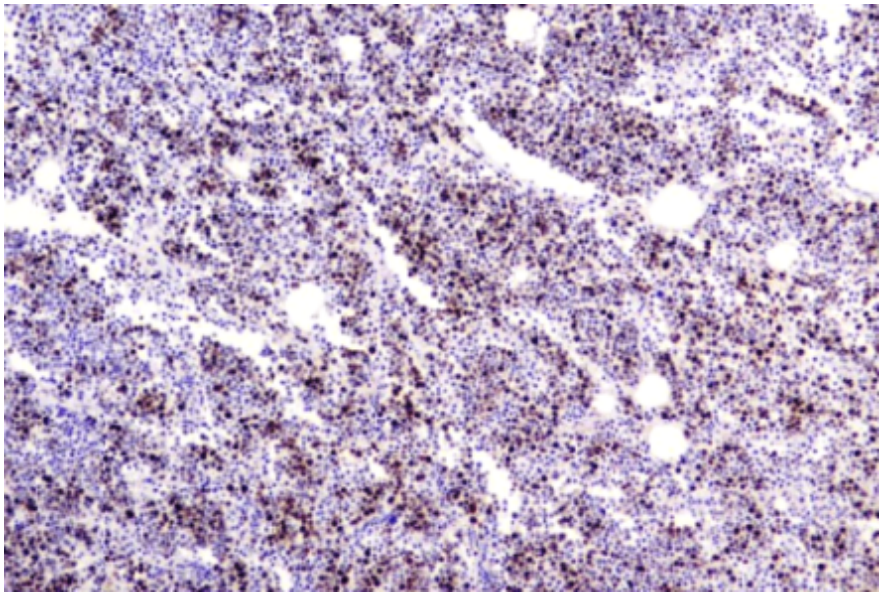


Figure 3: Immunohistochemistry showing tumor cells positive for CK, focally reactive for INSM-1, CD56, while being non-reactive for GATA3 (L 50-823). Ki-67(MIB-1) shows 40% of nuclear positivity.

Discussion:

The primary invasive breast carcinoma with neuroendocrine differentiation is a very rare type of breast tumor. Most commonly the neuroendocrine tumors are found in the gastrointestinal tract, pancreas, and bronchopulmonary system but rarely found in the breast (6). These tumors do not form the specific histopathological category of breast carcinoma but there are groups of breast carcinoma like ductal, lobular carcinoma, mucinous, and solid papillary carcinomas which can produce ectopic hormonal substances (7). There are three categories of neuroendocrine breast tumors as mentioned by the WHO in their 4^{th} revised edition.

- Well-differentiated,
- Poorly differentiated neuroendocrine/ small cell carcinoma, and
- Invasive breast carcinoma with neuroendocrine differentiation.

There is no specific radiological or clinical sign to diagnose the neuroendocrine tumor. Histopathological examination is the only means of making a definitive diagnosis. Grossly, the tumor is usually yellowish-colored with a firm consistency and multilobulated. (8) In this case, we found the tumor to be a gray-white lobulated structure. Histologically, the tumor usually shows similar features as neuroendocrine tumors of the gastrointestinal tract with nuclear palisading, cellular monotony, loss of cell cohesion, pesudorossete formation, and abundant eosinophilic cytoplasm and nuclei with stippled chromatin(9). Since the microscopic features are inconsistently present, IHC markers like chromatin A or B, synaptophysin, neurospecific enolase (NSE), CD-56, Ki-67, Leu 7(CD-57), INSM-1 are necessary for the diagnosis [12]. INSM and CD-56 were focally positive, and Ki-67 is around 40% with nuclear positivity.

This tumor should be differentiated from metastatic neuroendocrine tumors from extramammary sites. They may show features similar to the other primary tumors of the breast like lobular carcinoma and invasive ductal carcinoma in situ (2). Some markers like CK-7 and caudal-type homeobox-2(CD X-2) are useful to differentiate from GI neuroendocrine tumors. Usually, the neuroendocrine breast tumors are positive for CK-7 and negative for CDX-2 whereas in gastrointestinal neuroendocrine tumors CK-7 is negative and CDX-2 is positive (10).

Invasive breast carcinoma with neuroendocrine features is treated like other invasive carcinoma breast car-

cinomas. The primary treatment option is surgery depending upon the stage and location of the tumor. (1) The combination of mastectomy, axillary lymph node dissection, and metastasectomy is generally performed for surgical treatment. Like other breast carcinomas, they are treated by chemotherapy and radiotherapy. Immunohistochemistry helps to determine the type of adjuvant therapy (8).

Prognosis in the patient with breast carcinoma with neuroendocrine features generally depends upon the factors like age of the patient, axillary lymph node involvement, clinical-stage, hormonal receptors. (11) Neuroendocrine differentiation was said to be an independent adverse prognostic factor according to the multivariant analysis based on (Surveillance, Epidemiology, and End Results Program) SEER database. (5) In a retrospective comparative study by Zang et al., the breast carcinoma with neuroendocrine features showed a poorer survival rate, lower recurrence-free survival rate, and a high rate of distant metastasis. (12) Some literature reported that these tumors have a similar prognosis with invasive breast carcinoma when the clinical stage and grade of the tumors are compared. (13, 14)

Conclusion:

The histomorphology and the immunohistochemical study of the neuroendocrine markers are the basis for the definitive diagnosis of invasive breast carcinoma with neuroendocrine differentiation. But the combined approach with clinical assessment and radiological images aid in the diagnosis. The current diagnostic methods and treatment protocols are similar to other invasive breast carcinomas. Because it has a poorer prognosis than invasive carcinoma of the breast without neuroendocrine tumors, it is important to make the early diagnosis of the neuroendocrine component. Hence, larger studies are needed to better understand the biological features of invasive breast carcinoma with neuroendocrine differentiation.

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Ethical approval and consent to participate:

The hospital research board (HRB) of Nepal Cancer Hospital and Research Center, Harisiddhi, Lalitpur, Nepal provided approval.

Consent for publication:

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Conflicts of interest:

The authors declare that there is no potential conflict of interest with respect to the research, authorship, and /or publication of this article.

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None

Author's contribution:

KSA was involved in counseling, treatment of the patient and collection of CT-scan chest image. HPD and MS examined and interpreted the pathology. VA, KN, AM and MS collected the required case information, images, slides, and reports and contributed to writing manuscripts. VA, AM, KN, ASD and HPD reviewed the literature and contributed to both writing and editing the manuscript. All authors read and approved the final manuscript.

Data availability:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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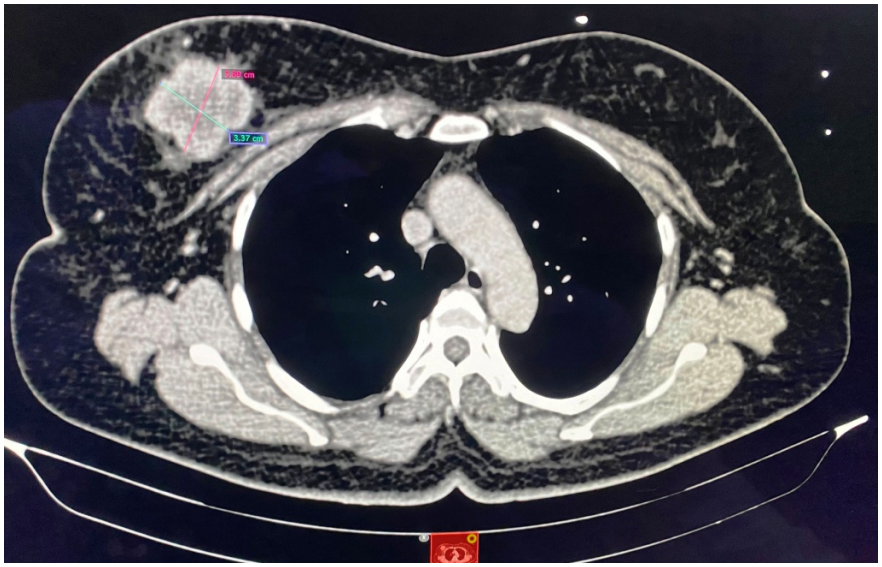

Figures:

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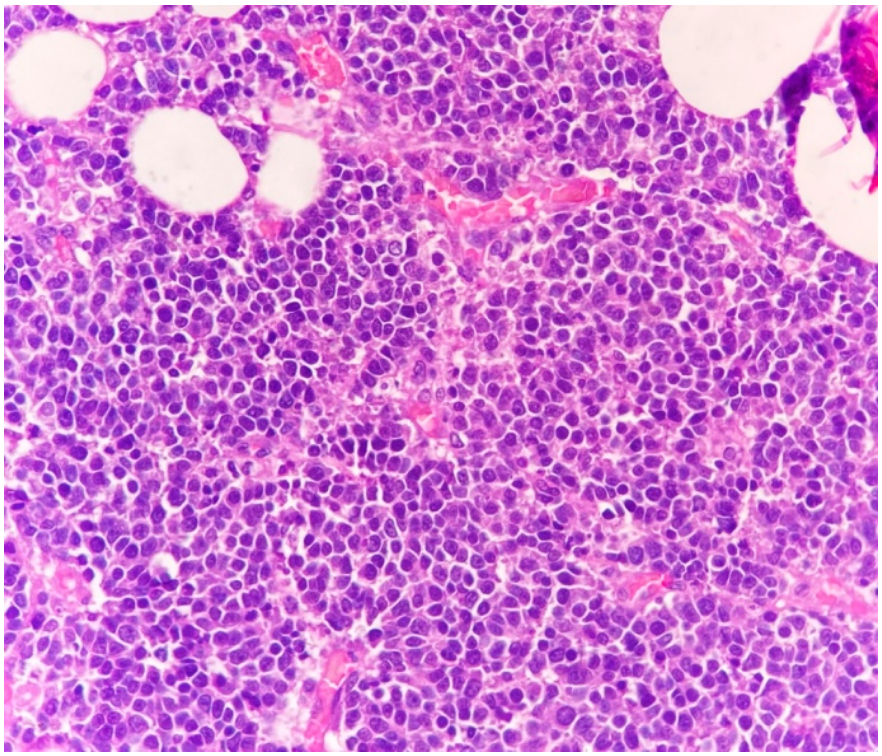

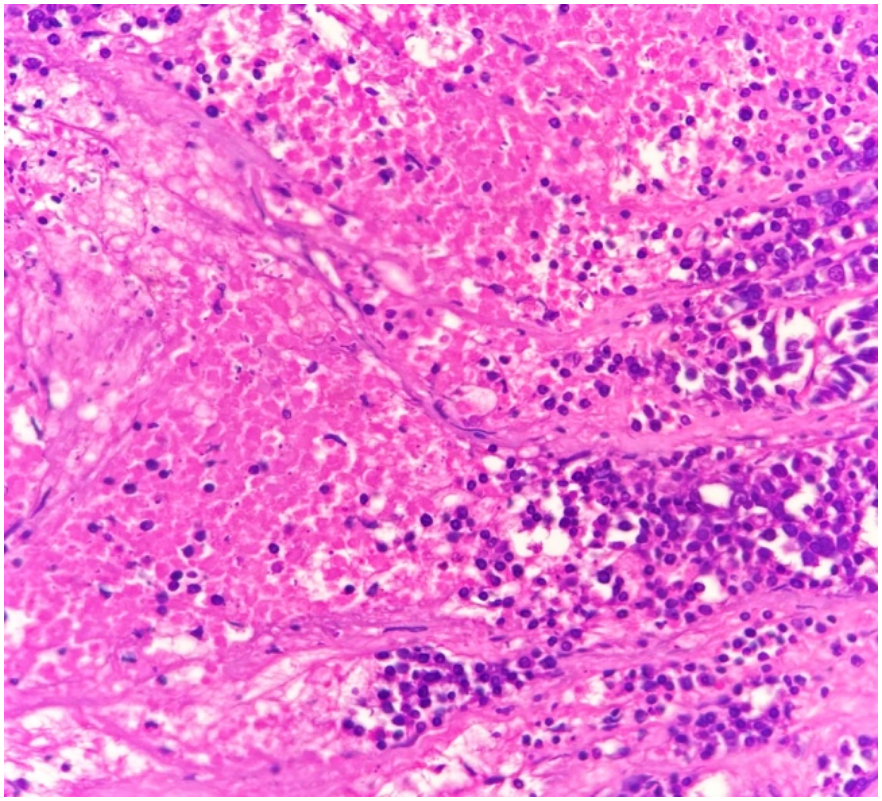

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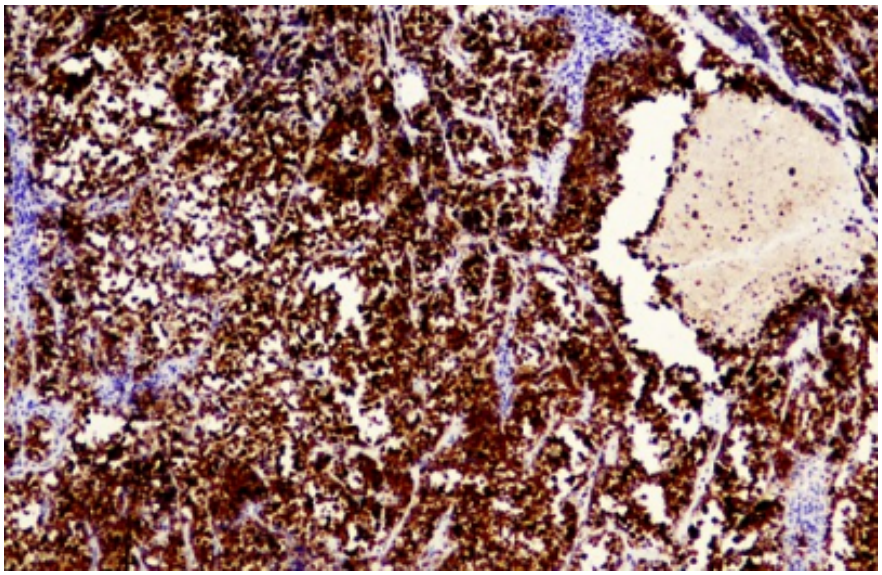

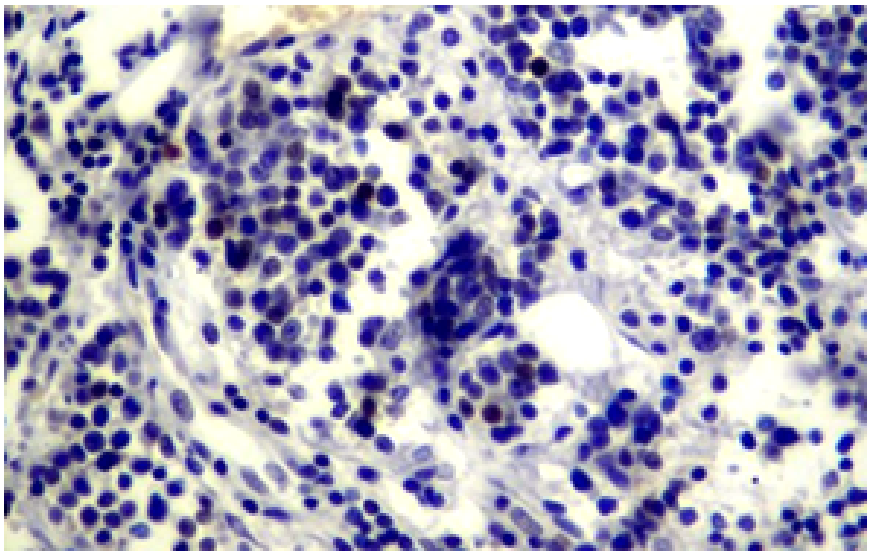

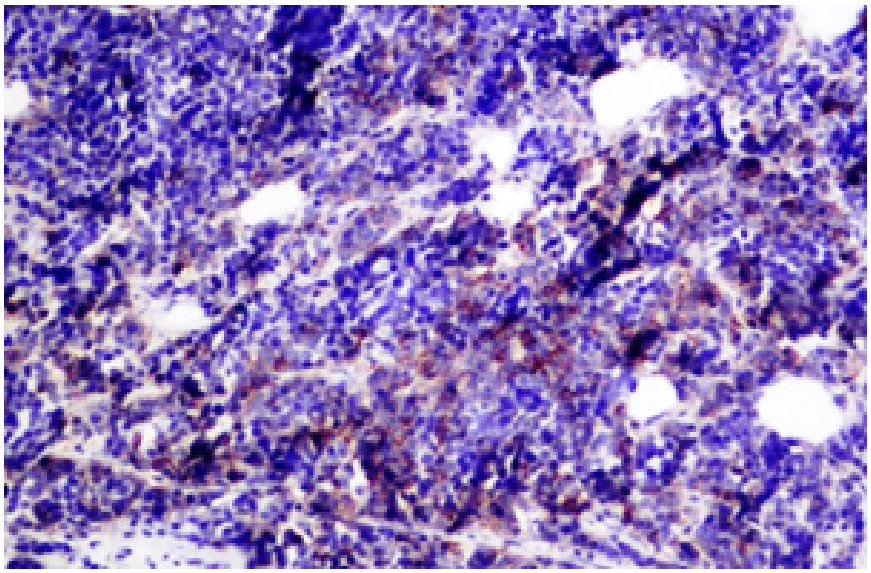

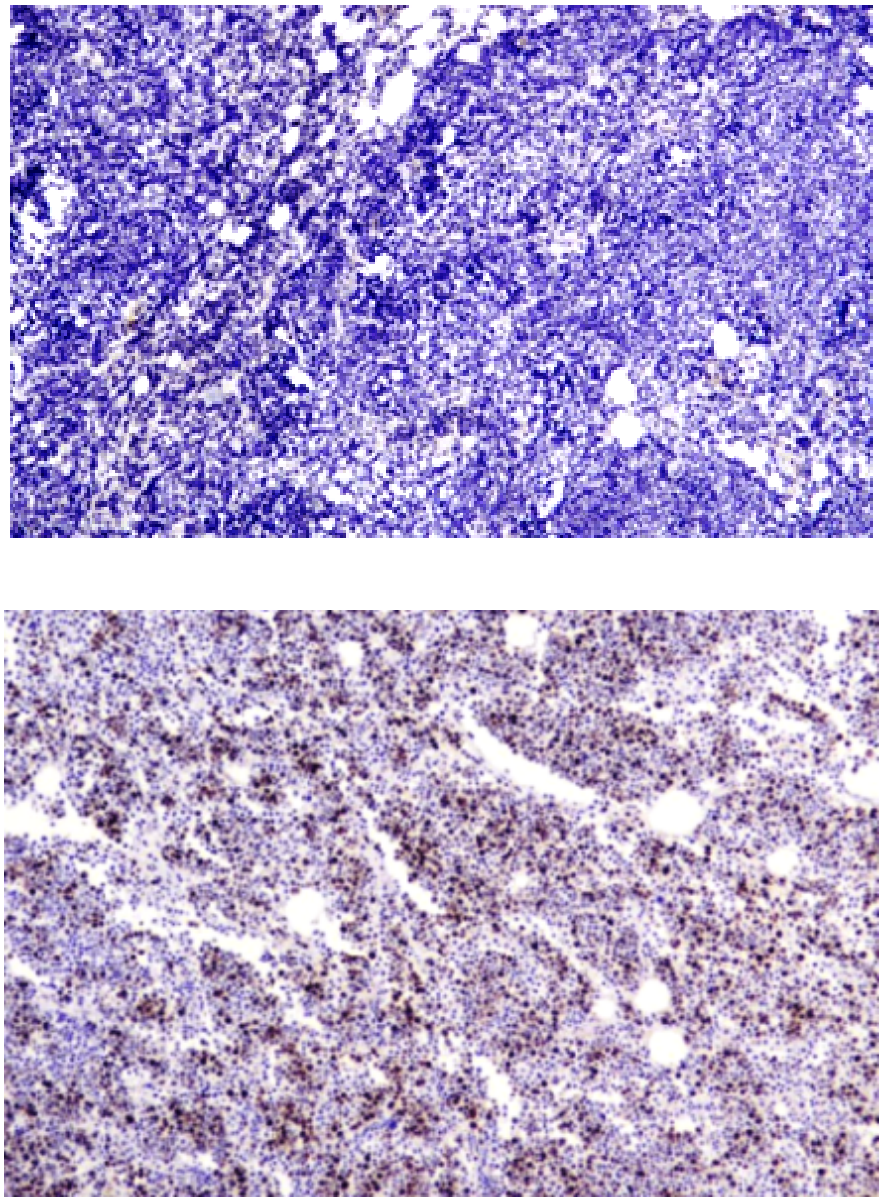

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