Thymic Neuroendocrine Tumor With Sjogren's Syndrome Cured by Neoadjuvant Chemotherapy and Thymectomy：A Case Report

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Case report

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Abstract

Background: Thymic neuroendocrine tumors are rare neoplasms usually accompanied with excessive secretion functional hormones of endocrine glands, such as multiple endocrine neoplasia 1(MEN1) and ectopic ACTH syndrome(EAS). As a kind of autoimmune disease, Sjogren's syndrome(SS) is characterized by destruction of exocrine glands resulting in oral and ocular dryness and is usually related to thymic lesion. However, we present herein a rare case of thymic neuroendocrine tumor with primary Sjogren's syndrome cured by neoadjuvant chemotherapy and thymectomy.

Case presentation: A 70-year-old woman was diagnosed as neuroendocrine carcinoma by puncture with Sjogren's syndrome(SS). Considering that the boundary between the tumor and the surrounding tissue is not clear，we chose two cycles of neoadjuvant chemotherapy which regimen was etoposide and cisplatin. After treatment, the symptoms of Sjogren's syndrome were partial relieved and therefore the patient underwent R0 resection. After one year of follow-up, apparent remission of the symptoms was achieved.

Conclusions: We believe neoadjuvant chemotherapy combined with radical surgery is an alternative treatment for locoregional resectable thymic neuroendocrine tumors. Because chemotherapy can lead to necrosis, it is a question whether the pathological grade of neuroendocrine tumors will be changed after neoadjuvant chemotherapy. Meanwhile, despite the fact that the association between thymic neuroendocrine tumors and Sjogren's syndrome remains unclear, the latter may be co-treated by oncologic therapy of the former，thus it also provides a new treatment for Sjogren's syndrome.

Background

Neuroendocrine carcinoma is a rare kind of cancer commonly originating in gastrointestinal tract, and through the literature review, it is more rarely published of mediastinal primary neuroendocrine carcinomas[1]. As a category of mediastinal primary neuroendocrine carcinomas, thymic neuroendocrine neoplasms(NEN) will be sometimes accompanied by endocrine diseases, such as multiple endocrine neoplasia1(MEN1) and ectopic ACTH syndrome(EAS)[2]. Sjogren's syndrome(SS) is a systemic autoimmune disease, characterized by lymphocyte infiltration and inflammation in the exocrine gland, especially in salivary and lacrimal, resulting in oral and ocular dryness[3]. SS is usually related to thymic lesion. Thymic hyperplasia, multilocular thymic cyst, thymoma associated with SS has been reported in the literature[4–6]. However, to our knowledge, the case of thymic NEN with SS has not been reported. In our study, we will report a case of thymic NEN with SS cured by neoadjuvant chemotherapy and thymectomy. After two courses of chemotherapy, the symptoms of SS such as dryness of the oral cavity and eyes, sleep disturbances, fatigue were partial relieved and SS was clinically cured after one year of follow-up.

Case Presentation

A 70 years old woman was found to have an abnormal mass in mediastinum on a chest computed tomography. Then she was admitted to our hospital for further treatment on March 31, 2017. Besides chest pain and distress, she complained of general fatigue and insomnia for 5 months. About 3 months ago, she felt a slightly dry mouth, and developed dry eyes and no tears after emotional excitement. About 1 months ago, the above symptoms were aggravated. The Schirmer test, unstimulated whole saliva flow rate, antibodies to Ro (SSA) and La (SSB) antigens, rheumatoid factor(RF) all showed abnormalities. According to the 2016 ACR/EULAR criteria[7], considering previous fitness, primary Sjogren's syndrome(pSS) was diagnosed. An enhanced chest computed tomography showed an upper-left mediastinal mass close to the upper lobe of left lung and the boundary with lung tissue, pericardium and peripheral great vessels being not clear with a small amount of pleural effusion, which was heterogenous with irregular border and calcification in size of 7.2×5.5cm (Fig. 1A). No other organs appeared to be affected on extensive examination, such as abdominal multiphasic CT, head CT, bone scan, etc. Screening for hormones in asymptomatic individuals is not routinely required, so specific hormones such as ACTH or somatostatin and others weren't tested. Percutaneous needle biopsy of the mediastinal mass showed neoplastic cells are arranged in flakes which stroma has thin-walled blood vessels. The cells contained fine chromatin and obsolete nucleolus. No conspicuous necrosis was identified. In a small biopsy sample, an accurate mitotic rate cannot be obtained, so the Ki-67 index is the preferred method of establishing the proliferative rate which was < 5% (Fig. 2A). Immunostains demonstrated the tumor had a neuroendocrine immunophenotype. Synaptophysin, chromograninA, and CD56 were positive (Fig. 2B, 2C, 2D). Based on the above characteristics, well differentiated neuroendocrine carcinoma was rendered. Considering the tumor may have violated pericardium, lung, peripheral great vessels which called Locoregional disease, the patient was started on etoposide 150 mg and cisplatin 30mg for 3 days per 21 days for 2cycles. No treatment-related toxicity was observed. The patient reported relief of chest pain, oral and ocular dryness. Especially, the quality of sleep and fatigue have been improved, so that the mental state was recovered in contrast with the original. We retested the antibodies against SS indicating negative RF but still positive SSA and SSB. A follow-up CT of the chest at the completion of her second chemotherapy regimen demonstrated necrotic foci of different sizes and a clearer boundary with the pericardium than before(Fig. 1B). The patient underwent a thymectomy with removal of part of pericardium(Fig. 3). The mass was completely removed. The surgical resection specimen showed a firm tumor measuring 6cm×2.5cm×3cm(Fig. 4). The histopathological findings indicated the mass invaded the extracapsular adipose tissue. Microscopically, postoperative hematoxylin and eosin (HE) staining showed > 10 nuclear mitosis per 10 HPF and frequent necrosis with a Ki-67 index of 20% (Fig. 2E). Based on the findings in the resection specimen, a diagnosis of high-grade neuroendocrine carcinoma was made. The patient was discharged in good clinical without other therapy, because of refusing further chemoradiation treatment. During one year follow-up, symptoms of oral and ocular dryness, fatigue were basically disappeared and insomnia is no longer controlled by drugs. Meanwhile, no evidence of disease recurrence was evident.

Discussion And Conclusions

Thymic NEN are rare tumours. Among Asian/Pacific islanders, their annual incidence has been reported to be approximately 0.04/100,000 population[8]. They account for 2% of all mediastinal tumours and 5% of all thymic tumours. The ratio of prevalence between male and female is 3:1[9]. Consequently, the rarity of thymic neuroendocrine neoplasms has resulted in few clear consensus statements or guidelines for optimal treatment. Howerer, the current evidence consistently suggests that thymic NEN behave in a more aggressive manner compared to NEN in other organs.

Thymic NEN are currently classified based on their histopathologic features as low-grade, intermediate-grade, high-grade neoplasms[10]. High-grade neuroendocrine carcinoma is different in mitoses per 10 HPF and necrotic degree compared with low-grade[11]. So, the reasons of differences in the morphologic and immunohistochemical features between the tumor in the biopsy and in the resection specimen were diversified. We guess the biopsy might have sampled a better-differentiated area which causes to degree of differentiation. The classification of thymus neuroendocrine tumors varies from that of gastrointestinal neuroendocrine tumors in some classification systems, and in particular does not include Ki-67 and includes the assessment of necrosis. It is worth noting that neoadjuvant chemotherapy can increase the necrosis of lesions, which may affect the pathological diagnosis of thymic NEN and the choice of follow-up treatment. Therefore, it is a question whether the pathological reclassification after neoadjuvant chemotherapy is meaningful for patients with thymic NEN treated with neoadjuvant chemotherapy.

As an autoimmune disease, SS is often accompanied by thymic lesion, such as thymic hyperplasia, multilocular thymic cyst, thymoma, as is reported. However, our patient was diagnosed as high-grade neuroendocrine carcinoma accompanied with pSS, as first presentation of thymic NEN. The mechanism we infer may be interaction between endocrine system and immune system which leads to destruction of acinar cells and the pathology contains thymic lymphoid hyperplasia which isn’t detected.

Neuroendocrine tumors are highly heterogeneous and all elements need to be considered (eg, histopathology, concomitant disease, symptoms). To date, no single currently available biomarker is sufficient as a diagnostic, prognostic, or predictive marker in patients with neuroendocrine tumors[12]. According to the relevant articles, the only unanimous prognostic factor is the completeness of surgical resection[2]. So, after multidisciplinary discussion, two cycles of neoadjuvant chemotherapy is preferred considering imaging features of lesions. Based on NCCN Guidelines of Neuroendocrine and Adrenal Tumors, cisplatin and etoposide are preferred regimens of adjuvant therapy.. Therefore, we chose EP neoadjuvant chemotherapy regimen. Fairly, after two courses of neoadjuvant chemotherapy, the symptoms of SS were partial relieved and RF turned negative. More importantly, the patient underwent R0 resection. Although literature data regarding the role of neoadjuvant chemotherapy in patients with potentially resectable NEN are not well defined[13], we think that it is an attemptable way for radical resection and relieving the symptoms of related complications. According to NCCN guidelines, after potentially curative surgery, surveillance is recommended for at least 10 years for most patients. Due to the loss of follow-up, our case was followed up for only one year, which is our deficiency.

For SS patients, fatigue is their most important symptom and the one most difficult to cope with, which is also the first symptom of our patient[14]. Previously, there is no ideal therapeutic drug for SS, mainly for local replacement therapy and systemic immunotherapy. And for related constitutional symptoms, there is currently no evidence to support pharmacological treatment. In our case, the symptoms of SS were relieved after two courses of chemotherapy and SS was clinically cured after one year of follow-up. So, we guess SS may benefit from neoadjuvant chemotherapy which aims to resectability of the tumor. Although the mechanism of association between thymic NEN and SS hasn't been explored, this provides a new treatment option for SS.

Abbreviations

MEN1: multiple endocrine neoplasia 1; EAS: ectopic ACTH syndrome; SS: Sjogren's syndrome; NEN neuroendocrine neoplasms; RF: rheumatoid factor; CT:computed tomography; pSS: primary Sjogren's syndrome; HE:hematoxylin and eosin.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Informed consent was obtained from the patient.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YBC, HFC, TYL and ZT performed the operation. HFC and TYL collaborated in the patient's perioperative care. HFC and DQ designed and drafted the manuscript. RW and YBC reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Figures

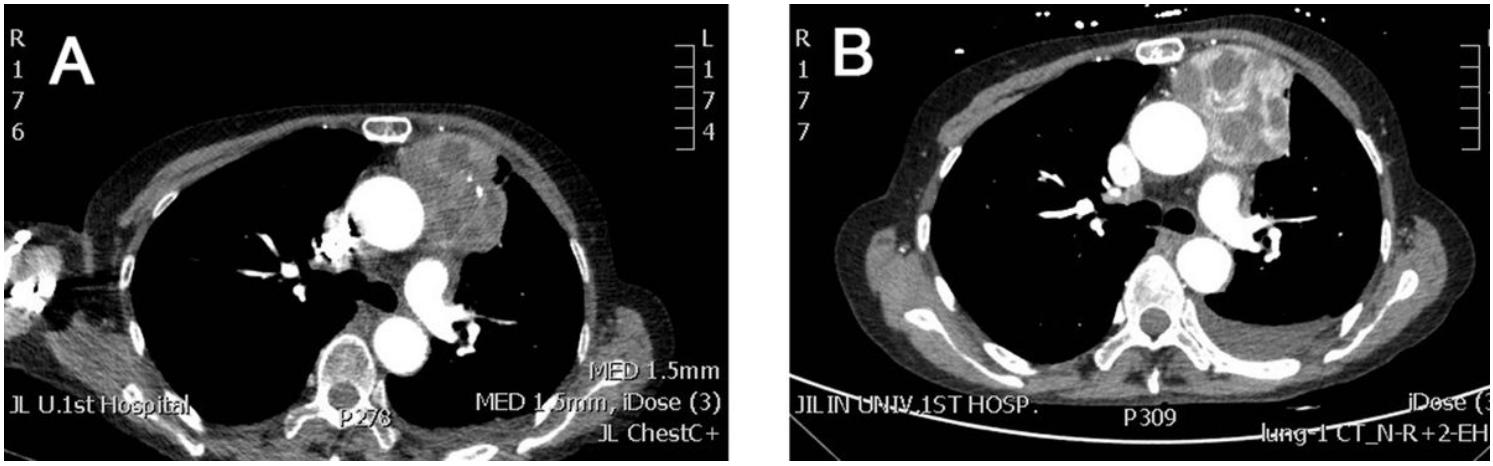

Figure 1

1A：Thoracic computed tomography (CT) scan revealed an upper-left mediastinal mass with unclear boundary about the surrounding tissue. 1B：A follow-up CT of the chest at the completion of his second chemotherapy regimens showing necrotic foci of different sizes and a clearer boundary than before.

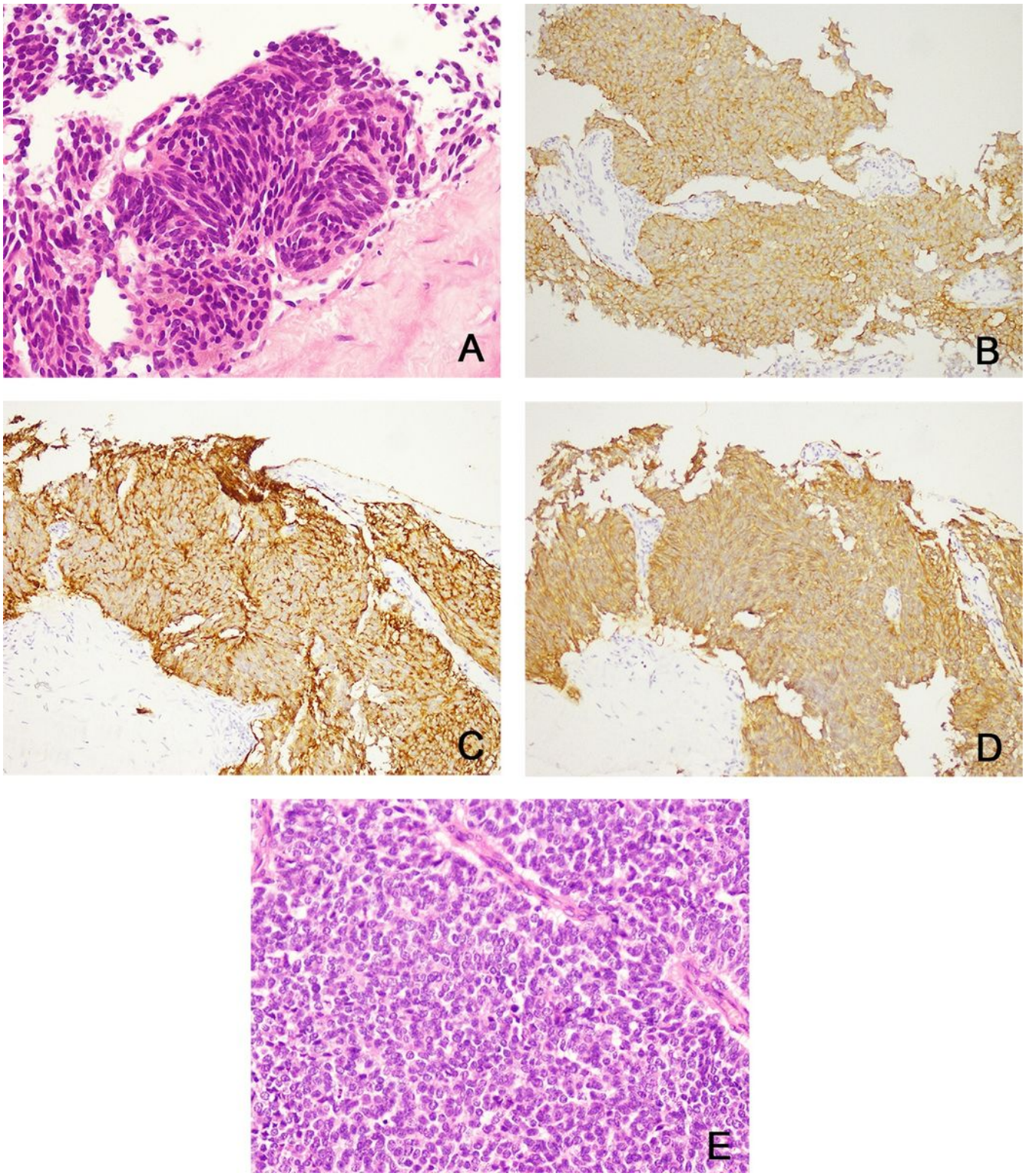

Figure 2

Percutaneous needle biopsy of the mediastinal mass showed the cells contained fine chromatin and obsolete nucleolus（hematoxylin-eosin, original magnification×400）（A） Immunohistochemical analysis was positive for Syn expression (×200) (B), CgA expression (×200) (C), CD56 expression（×200）(D). Postoperative pathological section revealed >10 nuclear mitosis per 10 HPF and frequent necrosis with a Ki-67 index of 20%（hematoxylin-eosin, original magnification×400）（E）.

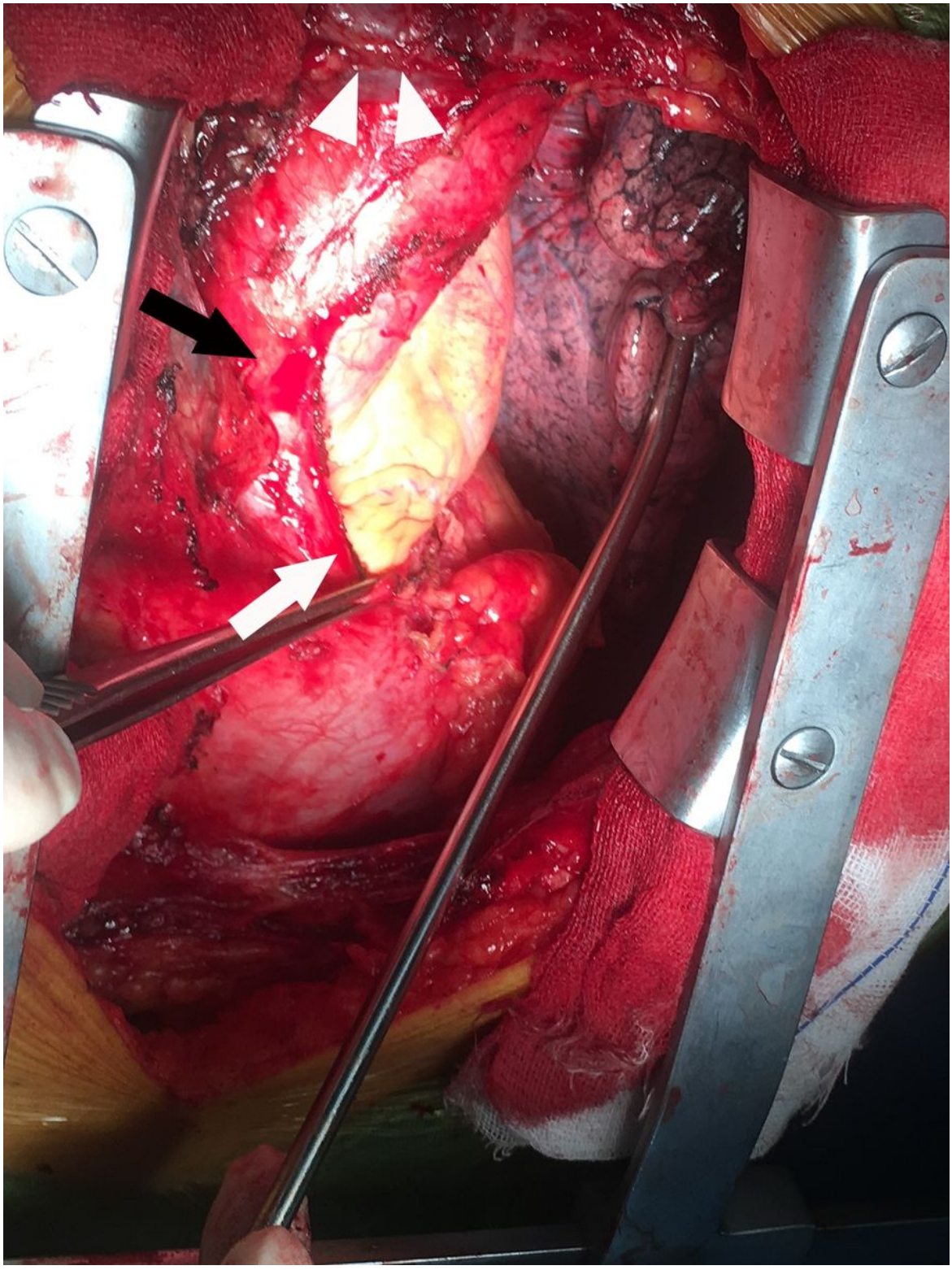

Figure 3

Intraoperative picture: Pericardium (white arrow);Left innominate vein (white arrowhead);Ascending aorta (black arrow)

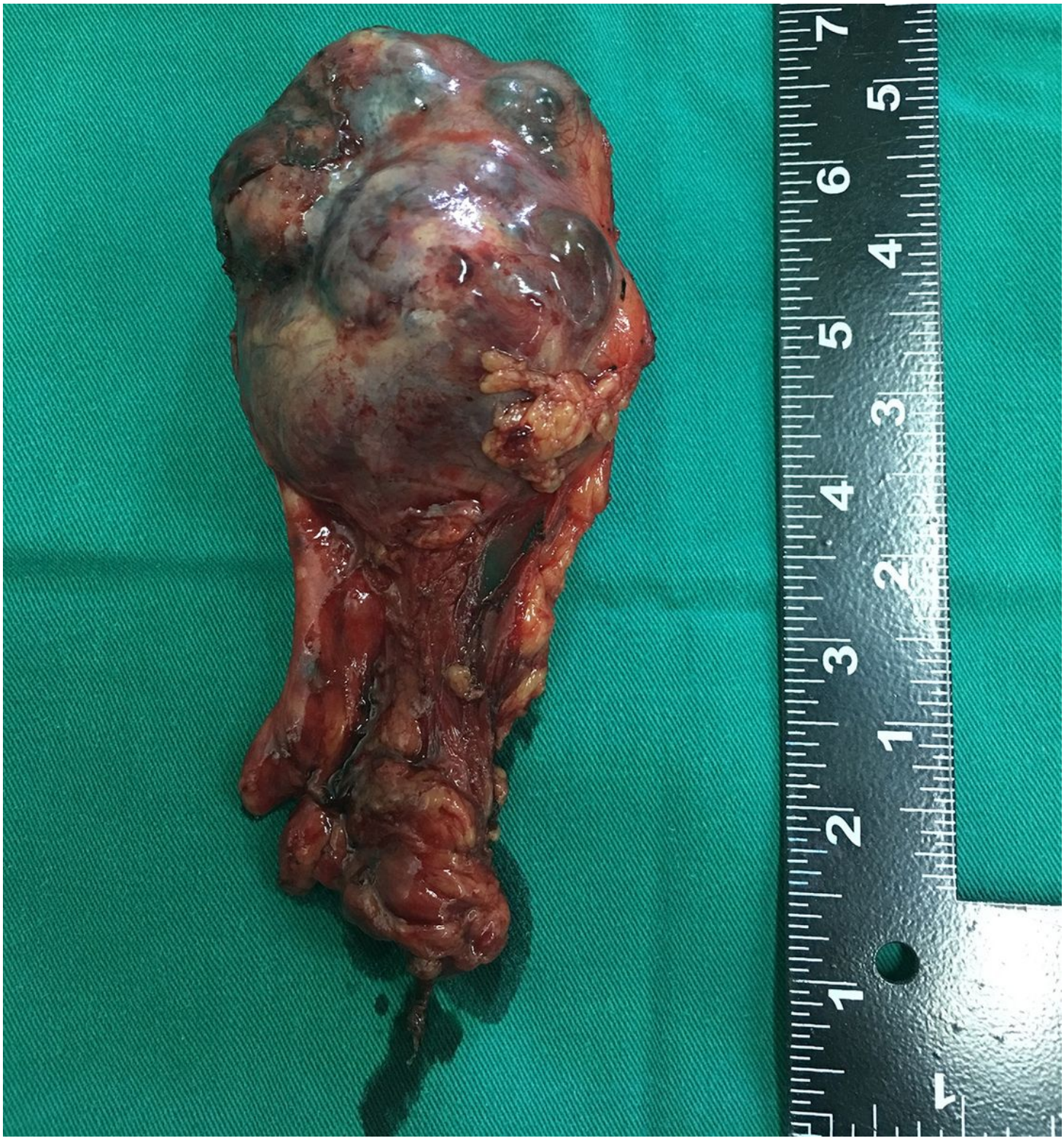

Figure 4

The surgical resection specimen showed a firm tumor measuring 6cm×2.5cm×3cm.