Paraganglioma with Hyperglycaemia as the Main Symptom: A Case Report.

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Case report

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Abstract

Background: Paraganglioma (PGL) is a rare neuroendocrine tumour derived from the extra- adrenal gland that is also known as ectopic pheochromocytoma (PHEO). The typical clinical symptoms are paroxysmal hypertension with headache, sweating and palpitation. However, PGL with abnormal glucose metabolism as the main manifestation is rare.

Case Presentation: In this case, the patient had a history of diabetes for 13 years and showed persistently increased blood glucose. The application of multiple hypoglycaemic drugs to control the patient's blood glucose was ineffective, and a limited effect of high-dose insulin was observed. This patient underwent a contrast-enhanced computed tomography scan(CT),showing a soft tissue density shadow (3.2×2.4cm) with clear edges and slight enhancement in the medial side of inferior vena cava. Exploratory laparotomy was performed and significant blood pressure changes were observed when the tumourwas removed during the operation. The patient's blood glucose decreased significantly and hypoglycaemiawas noted when the patient's original dose of insulin was maintained. The patient recovered uneventfully and was discharged after the operation.

Conclusions: Hyperglycaemia caused by PGL is rare in the clinic; therefore, it is necessary to pay attention to the relevant blood glucose indexes during the preoperative examination and diagnosis process to improve the examination process and further assist in the preoperative diagnosis of PGL. It is necessary to pay attention to changes in blood pressure during and after the operation to avoid hypoglycaemia. Lifetime follow up is necessary after the operation.

1. Background

Paraganglioma (PGL) is a pheochromocytoma (PHEO) occurring on the sympathetic and parasympathetic ganglia outside the adrenal gland that accounts for 10% of all cases of PHEO, with an incidence rate of approximately 0.01–0.02% and a malignant transformation rate of 2.4–14%. Some PGLs can produce hypertension, palpitations, hyperhidrosis and other symptoms because they secrete too much catecholamine. PGL is difficult to diagnose in the early stage, whereas hypertension, diabetes and hyperthyroidism are easily diagnosedclinically.PGL is a neuroendocrine tumour that is adjacent to the abdominal aorta and other large blood vessels. PGLis often misdiagnosed as retroperitoneal schwannoma, neurofibroma, ganglioneurocytoma, teratoma and so on. The preoperative diagnosis rate is only 2–3%. Surgical resection is the best treatment, and pathology is the gold standard for diagnosis. PGL may recur, and lifelong follow-up is required after operation. This paper summarizes and analyses the clinical data of a PGL patient with hyperglycaemia in order to further improve the clinical understanding of the disease.

2. Case Presentation

2.1 Patient information

The patient, a 62-year-old female, was admitted to the hospital for "13 years of hyperglycaemiaand more than 10 days of oedema in both lower limbs". Approximately 13 years ago, the patient was examined in the local hospital and found to have a fasting blood glucose of 28.5 mmol/l, without polyuria, dry mouth, polydipsia, fatigue, nausea and vomiting, limb numbness orblurred vision. The patient was diagnosed with "type 2 diabetes". The patient was treated with "metformin, Xiaoke pill" and other drugs to reduce her blood glucose level, without diet control. The patient experienced poor blood glucose control, with a self-test fasting blood glucose level of > 10 mmol/L. Seven years ago, "Novolin 30R, metformin, acarbose, pioglitazone" and other drugs were prescribed due to poor blood glucose control. The patient's fasting blood glucose was controlled at approximately 18 mmol/L. Three years ago, the patient began to have intermittent pain between the toes of both feet, described as needle-like; this pain was untreated. Half a year ago, due to poor blood glucose control, insulin ("Novolin 50R") was prescribed (24 units in the morning and 29 units in the evening via subcutaneous injection). The patient's self-reported fasting blood glucose level was approximately 14 mmol/L, with levels of 20 mmol/L after a meal, and there was no obvious oedema of the legs more than 10 days ago. The patient had a past history of "cerebral infarction" more than 4 years, without any sequelae. She also had a history of hypertension, which was diagnosed more than 4 years ago, but the patient's blood pressed was controlled without the regular use of oral antihypertensive drugs. Four years ago, the patient underwent surgery for a right fundus haemorrhage and recovered well.In addition, her haematological profile, such as the leukocyte, platelet, neutrophil and serum albumin levels, and her biochemical indicators (liver function, renal function, etc.) were within normal ranges. However, her glucose level was high (12.19 mmol/l). Tumourmarkers, for instance, alpha fetoprotein and carbohydrate antigen-199 (CA-199), were found to be normal, although the level of the tumour marker carcino-embryonic antigen (CEA) was slightly elevated (4.95 ng/ml; the normal range is 0-4.95 ng/ml in our hospital).Other endocrine indexes were basically normal and were as follows:angiotensinII20.81 pg/ml (25–250 pg/ml), aldosterone 49.71 pg/ml (70–300 pg/ml), renin activity 0.01 ng/ml (0.1–6.56 ng/ml), and urovanillic acid (VMA) 5.78 mg/24 h..

2.2 Imaging findings

Contrast-enhanced CT scan showed that the inferior vena cava could be visualized; it was compressed above the confluence level of both renal veins and the lumen was narrowed accordingly. At the level of the T12 vertebral body, a soft tissue density shadow was seen on the medial side of the inferior vena cava, with clear edges and slight enhancement. The maximum cross-sectional size was approximately 3.2 × 2.4 cm. No obvious enlarged lymph nodes were found in the retroperitoneum. A neurogenic tumour was considered in combination with the imaging findings (Fig. 1).The preoperative differential diagnosis was challenging, and we focused on schwannoma, neurofibroma and ganglioneurocytoma.

2.3 Therapeutic interventions

During the laparotomy, a 4 × 4 × 3 cm mass was found between the inferior vena cava and the abdominal aorta, and above the left renal vein into the inferior vena cava. The tumourwas tough and well defined (Fig. 2Aand2B). There were blood vessels between the tumour and the inferior vena cava and abdominal aorta. No enlarged lymph nodes were found around the tumour. When touching the tumour, the patient's

blood pressure increased significantly (systolic pressure increased rapidly from 120 mmHg to 240 mmHg), and the patient's heart rate also increased significantly (from 75th/min to 110th/min). The patient's blood pressure and heart rate decreased gradually more than 10 minutes after the administration of antihypertensive drugs. During the operation, care was taken to reduce the pulling and squeezing of the tumour body and completely remove the tumour(Fig. 2C).The patient's first blood pressure was 120 mmHg and her heart rate was 75–80 times/min.

2.4 Histopathological findings

Histologic examination showed a dark red round mass with a volume of 4 × 3.5 × 3 cm, which was coated on the surface, with grey red soft areas on section and necrosis in some areas (Fig. 2C). Immunohistochemistry showed positive expression of chromogranin(CgA) and synaptophysin(Syn), whereas S-100 and SMA expression was negative. In addition, a mitotic rate of approximately 1% was detectedby staining for the proliferative marker Ki-67 (Fig. 3) The diagnosis of PGL was confirmed.

2.5 Follow-up and outcomes

After the operation, the patient's condition gradually improved, and she recovered uneventfully. The patient was discharged from our unit and admitted to the Department of Endocrinology and the Department of Interventional Vascular Surgery for a diabetic foot. At the three-month, six-month, twelve-month and eighteen-month follow-up after surgery, there was no evidence of recurrence.

3 Discussion

Paraganglioma (PGL), also known as ectopic pheochromocytoma (PHEO), is a kind of neuroendocrine tumour derived from neural crest cells. Approximately 90% of PGLs can secrete catecholamine. Excessive secretion can cause paroxysmal or persistent hypertension, palpitations, hyperhidrosis, gastrointestinal dysfunction and other catecholamine syndromes, as well as serious heart, brain and kidney complications.[1, 2] PGL is mostly benign and less malignant. PGL can occur in all ages and in many parts of the body but is mainly distributed in the head, neck, mediastinum, retroperitoneum and other parts with paraganglion aggregation. Without a specific location, PGL is difficult to diagnose by ordinary CT.[3] According to the clinical manifestations, PGL can be divided into functional, subclinical and non-functional types. The clinical manifestations of functional PGL are paroxysmal or persistent hypertension and accelerated heart rate and are often accompanied by headache, dizziness, palpitations, sweating, anxiety and other symptoms. The classic clinical manifestations are paroxysmal hypertension with headache, sweating, and palpitations. Subclinical PGL is characterized by insufficient secretion of catecholamine, which produces clinical symptoms. There are usually no clinical manifestations of subclinical PGL. However, operation traction and compression can induce increases in BP, resulting in sharp fluctuations in blood pressure values that cannot be predicted before the operation, thereby increasing the difficulty of the operation and the risk to the patient. Non-functional PGL lacks typical symptoms and is only found when the tumour volume increases or a physical examination is performed. The patient in this study had a history of hypertension for many years, no history of regular oral

antihypertensive drugs, and good blood pressure control. The patient had no obvious hypertension before the operation, but her blood pressure fluctuated during the operation due to the stimulation of the tumour body; thus, she was diagnosed with subclinical retroperitoneal PGL.

The secretion of large amounts of catecholamine can also increase blood glucose levels, but PGL with abnormal glucose metabolism as the main manifestation is rare. The possible mechanism is that catecholamine secreted by the tumour can reduce insulin secretion, promote glucagon secretion, promote glycogen decomposition in the liver and muscle tissue and effect glucose absorption in the intestine. Recently, scientists from Japan used hyperglycaemic glucose clamp and hyperinsulinaemic normal glucose clamp technology to study PGL and found that the decrease in glucose tolerance caused by catecholamine section is mainly caused by altered insulin secretion, especially in the early stage of the insulin secretion response.[4] In this case, the patient had a history of diabetes for 13 years, and showed persistent increased blood glucose. The application of multiple hypoglycaemic drugs to control the patient's blood glucose was ineffective, and no effect of high-dose insulin was observed. Therefore, her increased blood glucose levels may have been related to the inhibition of insulin secretion by catecholamine released from the PGL.

Retroperitoneal PGL should be differentiated from schwannoma, neurofibroma, ganglioneuroma, solid pseudopapilloma of the pancreas, retroperitoneal sarcoma and giant lymphadenopathy. The initial diagnosis mainly depends on the imaging examination. Ultrasound, CT and MRI can be used as imaging examination modalities at the initial diagnosis. No specific manifestations are observed on ultrasound and this imaging modality is generally used as a means of postoperative follow-up. Contrast-enhanced CT can show the location, size, shape, blood supply and relationship with the adjacent tissues of the tumour. The sensitivity of the localization diagnosis of retroperitoneal PGL is 90%, although the sensitivity of MRI is better than that of CT. MRI shows a similar round or irregular mass. CT and MRI have advantages in the localization diagnosis of PGL, with accuracies of 80–95%, but the specificity is poor.[5, 6]Most PGLs secrete excessive catecholamine levels. The detection of catecholamine levels in plasma or urine and its metabolite, urovanillic mandelic acid, can provide the main basis for the qualitative diagnosis of PGL.[7]However, the levels of angiotensinII, aldosterone, renin and VMA in the urine were not increased in this case, and some of them were decreased, suggesting that even if the above results are negative, PGL cannot be completely ruled out.

It has been reported that patients with hyperglycaemia may account for more than 50% of PHEO/PGL patients. If the primary cause cannot be eliminated, the high levels of blood glucose will be difficult to control. Surgical resection of the tumour is the most effective method for treating refractory hyperglycaemia, and this condition should be actively treated. Because PGL has a complete capsule and abundant blood supply, it is necessary to carefully separate the tissues and blood vessels around the tumour during the operation to ensure the tumour is completely removed, avoid massive haemorrhage and reverse the flow of vasoactive substances into the blood. Meanwhile, it is necessary to gently operate in these cases to reduce pulling and squeezing of the tumour and avoid the risk of hypertension caused by the release of catecholamine from the tumour. For functional tumours, preoperative hypotension,

dilatation and correction of arrhythmias can reduce perioperative mortality.[1] After the operation, changes in blood glucose should be noted, and hypoglycaemic drugs should be adjusted in time to avoid the occurrence of serious hypoglycaemia. In this case, the patient's blood glucose levels were significantly improved after the tumour was removed. Hypoglycaemia occurred at her original treatment dose of insulin, indicating that the endocrine function of the tumour had a significant impact on the increased blood glucose levels. Hyperglycaemia caused by PGL is rarely seen in the clinic; therefore, it is necessary to pay attention to the relevant blood glucose indexes during the preoperative examination and diagnosis process to improve the examination process and further assist in the preoperative diagnosis of PGL. The diagnosis of PGLis based on pathological and immunohistochemical examinations. The combined application of CgA and Syn provides a reliable basis for the diagnosis of PGL. However, it is impossible to distinguish benign and malignant tumours using pathology and histology alone. The diagnosis of PGL should be based on the clinical biological behaviour of the tumour. LowKi-67 expression, a cell proliferation marker, is related to benign tumours and suggests that the prognosis of the patient is good.[8, 9]PGL may also be malignant. At present, the only conclusive evidence for the diagnosis of malignant PGL is metastasis.[10, 11] Therefore, long-term follow-up should be carried out to confirm whether the tumour is benign and malignant. PGL is not sensitive to radiotherapy and chemotherapy. Radiotherapy and chemotherapy are only used as analgesic treatment for metastatic tumours or to eliminate the residual tumour after operation. Operation is the only effective treatment for PGL. Patients should be followed up for life to monitor the recurrence of the tumour. If there is recurrence, the tumour should be resected again. Based on the theory that PGL involves multiple gene mutations, targeted therapy has become a new research hotspot. Some studies have shown that Hif-2α inhibitors, Everolimus, Sunitinib and other drugs, can be used for the effective treatment of the disease.[12–14]

In this study, the patient had hyperglycaemia in the early stage of the course of the disease, and she was resultantly misdiagnosed with type 2 diabetes mellitus. The clinician used a variety of hypoglycaemic drugs to try to control the patient's blood glucose level, but these drugs were unsuccessful. Additionally, there was no effect of high dose insulin on the control of the patient's blood glucose levels; however, neither PHEO nor PGL was suspected. PHEO and PGL patients often have a history of hypertension, and the conventional use of antihypertensive drugs often has poor efficacy. The patient in this study had a 4-year history of hypertension, and using a single antihypertensive drug or not taking antihypertensive drugs allowed her to control her blood pressure within the ideal range; thus, there was no doubt that the patient had PHEO or PGL. The diagnosis of PGL was not confirmed until the abdominal CT examination, which showed a lesion occupying the retroperitoneal space. An operation was performed, and PGL was confirmed by pathology after the operation. The misdiagnosis of PGL is based on the following: clinicians' lack of experience, lack of knowledge about atypical PGL, and narrow diagnostic thinking.

4 Conclusions

The accurate diagnosis of retroperitoneal PGL requires a comprehensive analysis of clinical symptoms, imaging manifestations and biochemical examination results. Surgical resection is the first choice of

treatment. The patients should be followed up for life at least once a year, including blood pressure, serum norepinephrine or urine catecholamine quantitative examinations and related imaging examinations. If recurrence is found, surgery should be performed again as soon as possible in combination with targeted drug treatment.

Abbreviations

PGL=Paragangliom, PHEO=pheochromocytoma□CT=computed tomography, CA-199=carbohydrate antigen-199, CEA=carcino-embryonic antigen, VMA=urovanillic acid, CgA=chromogranin, Syn=synaptophysin

Declarations

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Authors' contributions

Yanbin Wu and Lingqun Kong conducted the literature review and drafted the manuscript. Yu Cheng and Qiangpu Chen provided the relevant images. Chenglong Gou and Xuewen Wang collected the clinical data. Xingyuan Zhang and Xuefeng Cao revised the manuscript and figures. All authors approved the final version of the manuscript.

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Availability of data and materials

All data and material are fully available without restriction.

Ethics approval and consent to participate

Informed consent was obtained in writing from the patients and is available for review by the editor.

Consent for publication

Written informed consent for publication was obtained from the participant.

Competing interests

The authors declare that they have no conflict of interest.

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Figures

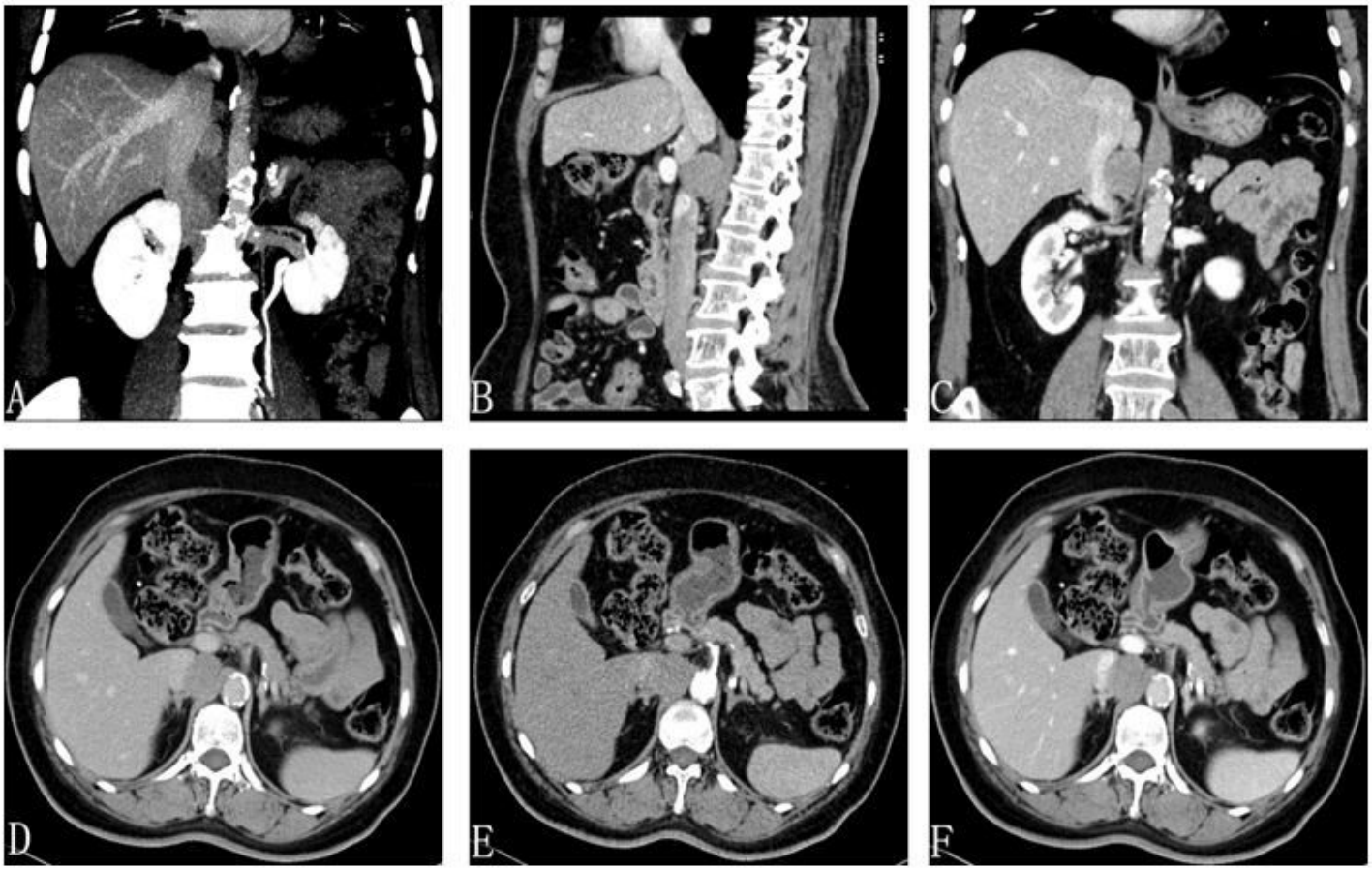

Figure 1

Contrast-enhanced CT scan showing a mass in the abdominal cavity (A-F)

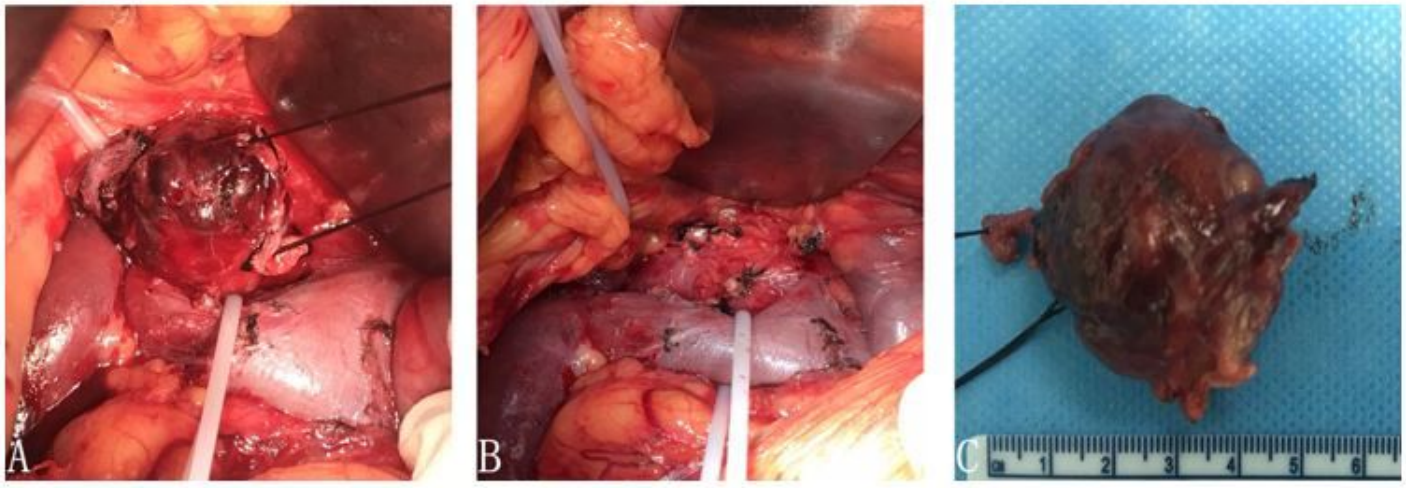

Figure 2

Photographs of the tumour. (A) Surgical exposure of the tumour; (B)Abdominal cavity after tumour resection ;(C) Removal of the tumour mass

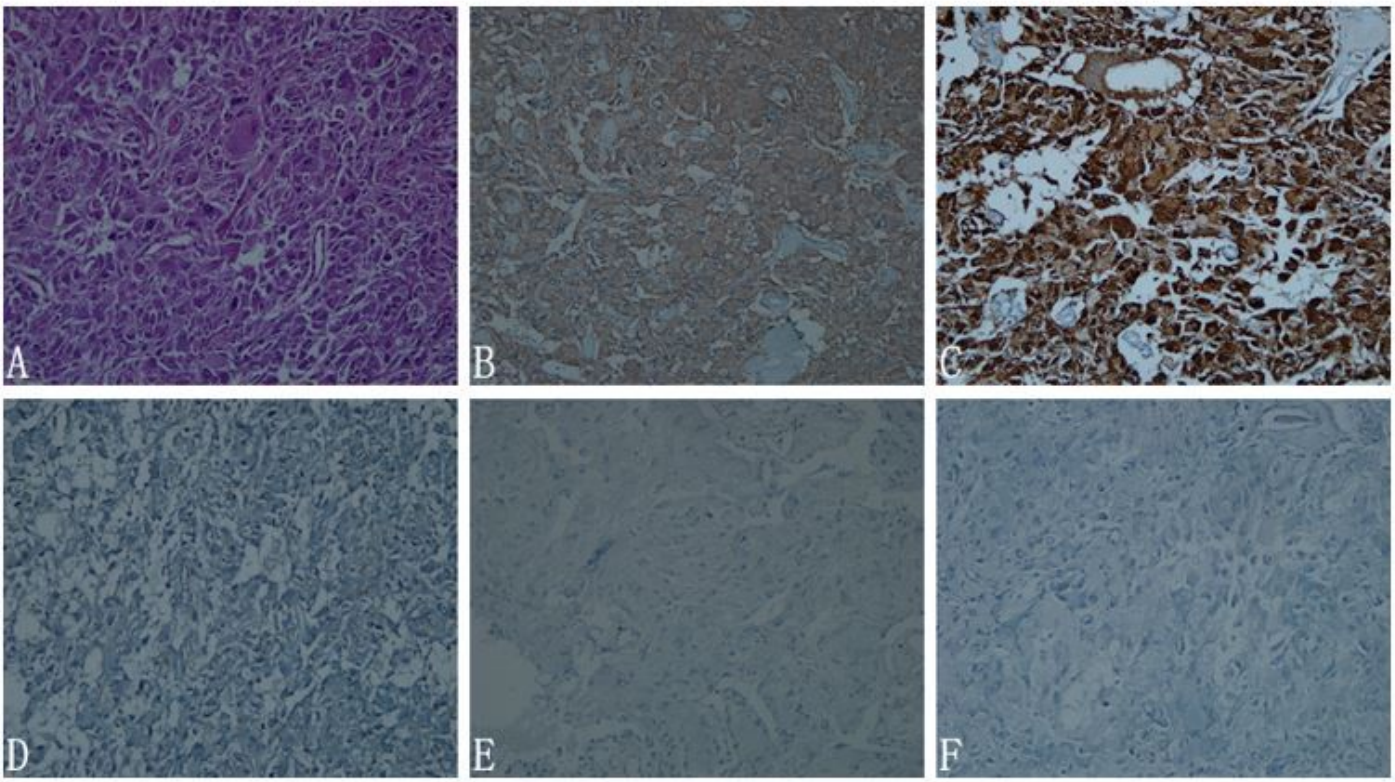

Figure 3

Immunohistochemistry findings of the postoperativespecimen (A-F). (A)Haematoxylin-eosin(HE)staining (x200);Tumour cells were positive for Syn(B) and CgA (C)but negative for S-100 (D) and SMA(E) (x200); (F) The Ki-67-positive ratewas approximately 1%(x200).