Ectopic ACTH Syndrome and Hypothyroidism Due to Right Renal Small Round Blue Cell Tumor: A Case Report

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Case Report

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Abstract

Background: Small round blue cell malignancies are rare and highly aggressive tumors that are commonly located in the soft tissues or axial bones of the bone or trunk and are particularly rare in the kidney. The common cause of ectopic ACTH syndrome is pulmonary neuroendocrine tumors, such as small cell carcinomas and carcinoid tumors. Here, we present an unusual case of ectopic ACTH syndrome and hypothyroidism caused by small round blue cell tumor of the right kidney.

Case presentation: A 19-year-old girl presented with a history of right lumbar pain and discomfort for 2 months, aggravated for 2 days. Abdominal contrast-enhanced computed tomography and computed tomography angiography showed right suprarenal pole occupancy with subepithelial hemorrhage. Preoperative hormone levels including plasma total cortisol (PTC), adrenocorticotrophic hormone (ACTH) and thyroid hormone measurements were abnormal, indicating that the patient had Cushing syndrome and hypothyroidism. The patient underwent right radical nephrectomy. Histopathological analysis revealed a renal small round blue cell tumor (consistent with a primitive neuroectodermal tumor), with positive immunohistochemistry for CD99 and Ki67 (about 10%) and molecular pathology for EWSR1 gene fusions. PTC, ACTH and thyroid hormone returned to normal after surgery.

Conclusions: We report a rare ectopic ACTH syndrome and hypothyroidism due to renal small round blue cell tumor. The clinical manifestation of renal small round blue cell tumor is non-specific and the diagnosis relies on pathological morphology, immunohistochemistry and fusion gene detection. At present, surgery combined with radiotherapy and chemotherapy is used in the treatment, but the prognosis is still not optimistic.

Background

Small round blue cell tumors are a rare class of malignant tumors that can occur in all parts of the body, most commonly in bone or soft tissues in the trunk or axial bones, and rarely in the kidney(1, 2). Small round blue cell tumors are histologically characterized by proliferation of small round tumor cells with sparse cytoplasm, which are often difficult to distinguish by standard histology or immunohistochemistry(3, 4). The disease usually has an insidious onset, rapid progress, easy recurrence and metastasis, and poor prognosis. Patients with small round blue cell tumors require rapid treatment(5).

Cushing syndrome caused by excessive secretion of ACTH from tumor tissues other than the pituitary gland is called ectopic ACTH syndrome, accounting for 10%-20% of Cushing syndrome(6). The common causes of ectopic ACTH syndrome are lung or bronchial tumors, followed by thymic and pancreatic tumors(7). Herein, we introduce a rare case of ectopic Cushing syndrome and hypothyroidism caused by a malignant tumor of small round blue cell in the right kidney.

Case Presentation

A 19-year-old girl presented to our hospital with a history of right lumbar pain and discomfort for 2 months and aggravated for 2 days. The patient felt the right waist pain 2 months ago, which was persistent dull pain, and increased right-sided back pain after running 2 days ago. Abdominal computed tomography (CT) showed right renal hamartoma with hemorrhage in the local hospital. The patient had no significant medical history and was not receiving any medication at the time of referral. Of note in the history was that the patient discovered facial swelling, increased acne on the face and back, and scanty menstruation six months ago. Upon admission, physical examination revealed concentric obesity and positive percussion pain in the right costal horn.

Laboratory Examination

Blood routine (Sep 5): white-cell 17.15 × 10^9/L, neutrophil 16.01 × 10^9/L, neutrophil percentage 93.3%. Renal function (Sep 5): urea nitrogen 4.6 mmol/L, creatinine 52 umol/L. Liver function (Sep 5): total protein 60.5 g/L, albumin 34.5 g/L. Thyroid hormone (Sep 5): triiodothyronine 0.638 nmol/L, thyroxine 64.37 nmol/L, free triiodothyronine 1.62 pmol/L, free thyroxine 10.26 pmol/L, thyroid stimulating hormone 0.847 uIU/mL. Female hormones (Sep 6): dehydroepiandrosterone sulfate > 1000

ug/dL, sex hormone binding globulin 12.6 nmol/L, cortisol > 60 ug/dL. Cortisol rhythm (Sep 6): cortisol 82.255 ug/dL (8: am), cortisol 92.705 ug/dL (4: pm), cortisol 65.859 ug/dL (12: pm). Adrenocorticotrophic hormone (ACTH) rhythm (Sep 6): ACTH 231,756 pg/mL (8: am), ACTH 242.763 pg/mL (4: pm), ACTH 202.883 pg/mL (12: pm). (Table 1)

Table 1
Changes in patients' laboratory examination results.

	Normal Ranges	Sep 5	Sep 6	Sep 7	Sep 8 (8:00 am)	Sep 8 (5:00 pm)	Sep 9	Sep 10	Sep 11	Sep 21
Blood routine										
White-cell (10^9/L)	3.5–9.5	17.15	24.1		19.87	26.74	11.36	8.89	6.69	7.41
Red-cell (10^12/L)	3.8–5.1	4.75	4.61		4.25	3.24	2.84	2.85	2.59	3.39
Hemoglobin (g/L)	115–150	145	143		130	98	86	85	78	101
Platelets (10^9/L)	125–350	197	168		106	137	90	67	58	262
Neutrophil count (10^9/L)	1.8–6.3	16.01	22.56		19.12	25.65	10.37	7.66	5.78	5.35
Neutrophil percentage (%)	40–75	93.3	93.61		96.24	95.9	91.31	86.21	86.5	72.11
Renal function										
Urea nitrogen (mmol/L)	2.9–7.2	4.6	7.6	9.9		10.6	11.3	8.9	7.2	8.2
Creatinine (umol/L)	53–132	52	117	124		146	155	137	116	112
Uric acid (umol/L)	150–360	180	223	239		321	378	296	312	393
Liver function										
Total protein (g/L)	66.0–83.0	60.5	56.2	55.2		36.2	42.3	45.8	50.2	73.9
Albumin (g/L)	40.0–55.0	34.5	36.8	33.8		24.3	30.3	33	34.4	47.1
Globulin (g/L)	20.0–40.0	26	19.4	21.4		11.9	12	22.8	15.8	26.8
Thyroid Hormone										
Triiodothyronine (nmol/L)	1.23–3.08	0.638							0.582	1.365
Thyroxine (nmol/L)	65.64-181.47	64.37							78.99	94.287
Free triiodothyronine (pmol/L)	2.77–7.08	1.62							1.86	4.35
Free thyroxine (pmol/L)	11.97–21.88	10.26							14.84	18.14
Thyroid stimulating hormone (ulU/mL)	0.27–4.2	0.847							3.9	2.26
Female hormones										
Follicle stimulating hormone (mlU/mL)	4.6–8.6		4.77							6.96

	Normal Ranges	Sep 5	Sep 6	Sep 7	Sep 8 (8:00 am)	Sep 8 (5:00 pm)	Sep 9	Sep 10	Sep 11	Sep 21
Luteinizing hormone (IU/L)	1.5-7.0		3.75							7.64
Estradiol (pg/mL)	18–63		47							34
Testosterone (ng/mL)	0.15–0.51		2.13							0.24
Prolactin (ng/mL)	3.5–24.2		15.72							16.69
Dehydroepiandrosterone sulfate (ug/dL)	51–321		> 1000							167.2
Sex hormone binding globulin (nmol/L)			12.6							49.2
Cortisol (ug/dL)	8.7–22.4		> 60							12.44
Cortisol rhythm										
Cortisol (8:am) (ug/dL)	4.26–24.85		82.255					11.495		17.762
Cortisol (4:pm) (ug/dL)	1.9–17.3		92.705					5.847		6.107
Cortisol (12:pm) (ug/dL)			65.859					6.088		2.921
ACTH rhythm										
ACTH (8:am) (pg/mL)	7.2–63.3		231.756					36.489		34.742
ACTH (4:pm) (pg/mL)	3.6–31.7		242.763					30.08		25.388
ACTH (12:pm) (pg/mL)			202.883					22.947		35.454

Imaging Examinations

Abdominal imaging with contrast-enhanced computed tomography and computed tomography angiography (Sep 5) showed right suprarenal pole occupancy (size 9.4cm*9.9 cm) with subepithelial hemorrhage, right renal artery branch supplied blood, and the right portal lymph node enlargement (Fig. 1).

Treatment

Re-examination of the patient's blood routine, renal function and protein level showed that the infection index further increased, and the renal function and protein level decreased. The patient received double J tube implantation under left ureteroscope plus right radical nephrectomy plus clearance of right perirenal hematoma plus lysis of right perirenal adhesion on Sep 8. The patients were transferred to ICU monitoring and treatment after surgery.

Pathology

The maximum diameter of the tumor was 8 cm. The tumor involved renal parenchyma, perirenal adipose tissue and adrenal gland, and a carcinoma thrombus was seen in the vasculature. Under light microscope, the tumor cells were lamellar, composed of a large number of small round cells with relatively uniform morphology and little cytoplasm (Fig. 2). The immunohistochemical results were positive for CD99 and Ki67 (about 10%), while Vim, Syn, FSH and ACTH were negative (Fig. 3). EWSRI gene fusion was detected by fluorescence in situ hybridization (FISH) (Fig. 4). According to the results of postoperative pathology and molecular pathological examination, the finally diagnosed was renal small round blue cell tumor (consistent with primitive neuroectodermal tumor (PNET)).

Follow-up

The blood routine, renal function and protein levels of the patients showed a trend of improvement for three consecutive days after surgery, ACTH and plasma total cortisol (PTC) decreased to normal, and thyroid hormones tended to normal (Table 1). The patient's facial swelling was reduced and the acne on her face and back subsided. However, three weeks after surgery, the patient died while preparing for further chemotherapy.

Discussion And Conclusions

PNET is a highly malignant small round blue cell tumor with neural differentiation. According to the location, PNET can be divided into central PNET (cPNET) and peripheral PNET (pPNET)(8). PNET usually occurs in children and adolescents, and the most common site is bone or soft tissue in the trunk or axial bone. PNET in the genitourinary system is relatively rare, and even rarer in the kidney(9). Renal PNET is a type of pPNET with a median age of about 27 years old, and is slightly more common in males(10).

The clinical manifestations of renal PNET are non-specific. The gross section of tumor tissue was gray, grayish brown and tender, accompanied by hemorrhage, necrosis and cystic degeneration. In the histological examination of renal PNET, the tumor cells were arranged in nest shape, and Homer-Wright rosettes were seen. Homer-Wright rosettes are one of the main histological bases for the diagnosis of renal PNET(11). The diagnosis of renal PNET mainly depends on pathological examination. With the improvement of immunohistochemical techniques, immunohistochemistry has become an important basis for pathological diagnosis of renal PNET(12). CD99 is a monoclonal antibody that recognizes p30/32 glycoprotein and can be detected in almost all renal PNET(13). In addition, some cases expressed vimentin, NSE, S-100 and Syn(14). There is no standardized criteria for the pathological diagnosis of renal PNET, which is generally considered to be consistent with(15): (1) Homer-Wright rosettes under light microscope; (2) positivity for CD99 and other neural markers (at least 2 kinds).

In recent years, it has been found that 90%-95% of PNET have a t(11; 22) (q24; q12) chromosome translocation, leading to the production of the EWS/FLI-1 fusion gene(16). It has been shown that the FISH method detects EWSR1 gene fusions with a sensitivity of 92.3% and a specificity of 100%(17). Therefore, the FISH method to detect fusion genes formed by PNET-specific chromosomal translocations has greater diagnostic and differential diagnostic value. In summary, the diagnosis of renal PNET should be comprehensively judged by light microscopic morphology, immunohistochemistry and FISH method. In the pathological diagnosis of this patient, immunohistochemistry showed CD99 and Ki67 positivity, FISH showed EWSR1 gene fusion, and the diagnosis of small round blue cell tumor was confirmed.

According to previous reports, ectopic ACTH syndrome is primarily associated with small cell or lung carcinoid carcinoma, and also be associated with mediastinum, pancreases, thymus, and pheochromocytoma(18–20). Neuroendocrine tumors rarely produce excessive ACTH and cause ectopic ACTH syndrome. To our knowledge, we describe the first case of ectopic ACTH syndrome and hypothyroidism caused by a renal small round blue cell tumor. Although our patient received radical nephrectomy treatment, postoperative ACTH and PTC decreased to normal, and thyroid hormones tended to normalize. The patient's facial swelling was alleviated and the acne on the face and back subsided. However, due to the highly malignant and aggressive nature of the tumor, the patient died in preparation for further chemotherapy.

Renal PNET is more prone to recurrence and metastasis than other renal tumors, with the most common site of metastasis being the lung, followed by the liver and bone(21). 1/3 of patients have a renal vein or inferior vena cava thrombus at the time of diagnosis, which makes treatment often ineffective. The prognosis of renal PNET is generally poor, with a 5-year overall survival rate of approximately 45–55%(5). Due to the rarity of renal PNET, there is no uniform standard of treatment for renal PNET. Renal PNET is still a rare tumor, and more cases need to be accumulated to explore better treatment options.

Abbreviations

PNET, Primitive neuroectodermal tumor, PTC, Plasma total cortisol, ACTH, Adrenocorticotrophic hormone, CT, Computed tomography.

Declarations

Ethics Approval and Consent to Participate The study was in line with the Helsinki Declaration and approved by the Ethics Committee at the Affiliated Zhongda Hospital of Southeast University. The study outcomes will not affect the future management of the patients. The use of human blood samples was in accordance with the legislation in China. Informed consent was obtained from the controls and patients or their relatives.

Consent for publication Written consent was obtained from the patient to publish this case report.

Availability of data and materials The dataset used during the study are available from the corresponding author on a reasonable request.

Conflicts of Interest We declare that there are no conflicts of interest between authors.

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Authors' contributions WM, LZ and MC designed the research. WM, JX and YW performed the research and analyzed results. WM, JX and HL wrote the paper. WM, LZ and MC edited the manuscript and provided critical comments. All authors read and approved the final manuscript.

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Figures

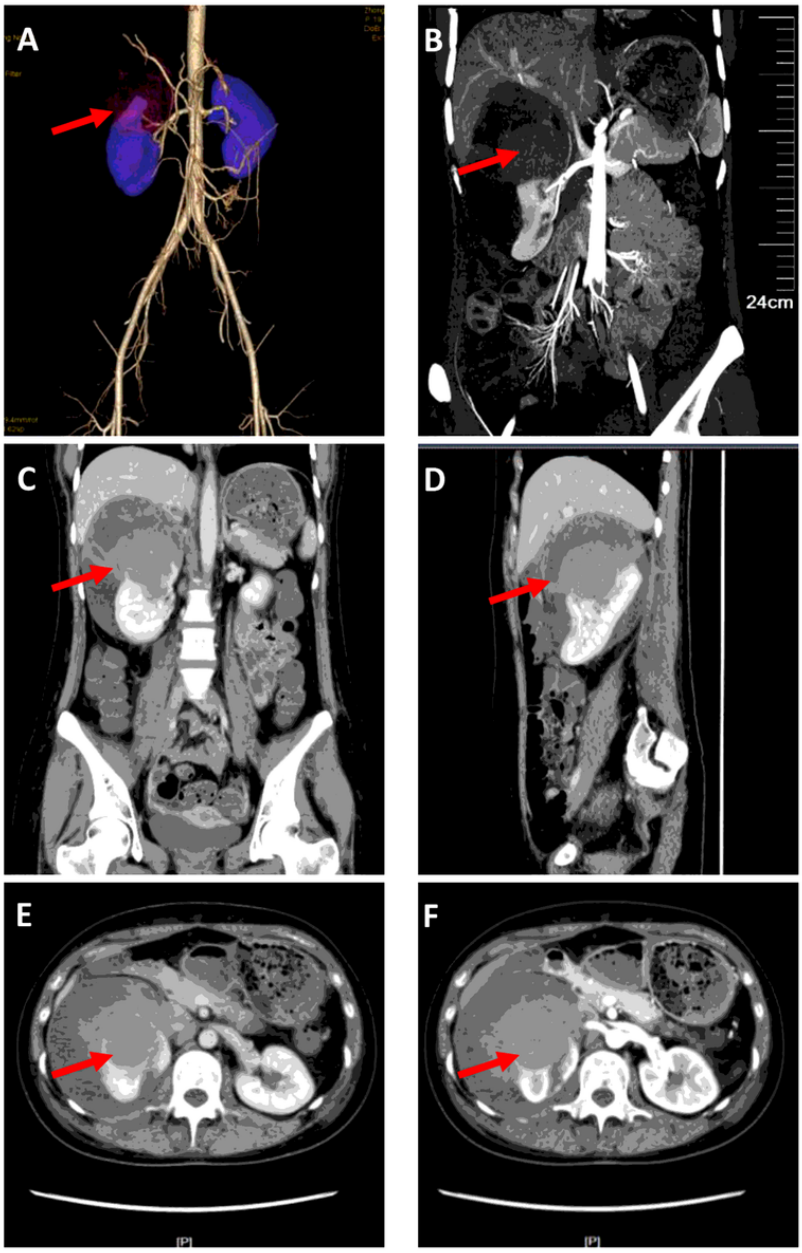

Figure 1

Abdominal imaging with contrast-enhanced computed tomography and computed tomography angiography images. A and B, Computed tomography angiography images; C-F, Abdominal imaging with contrast-enhanced computed tomography images.

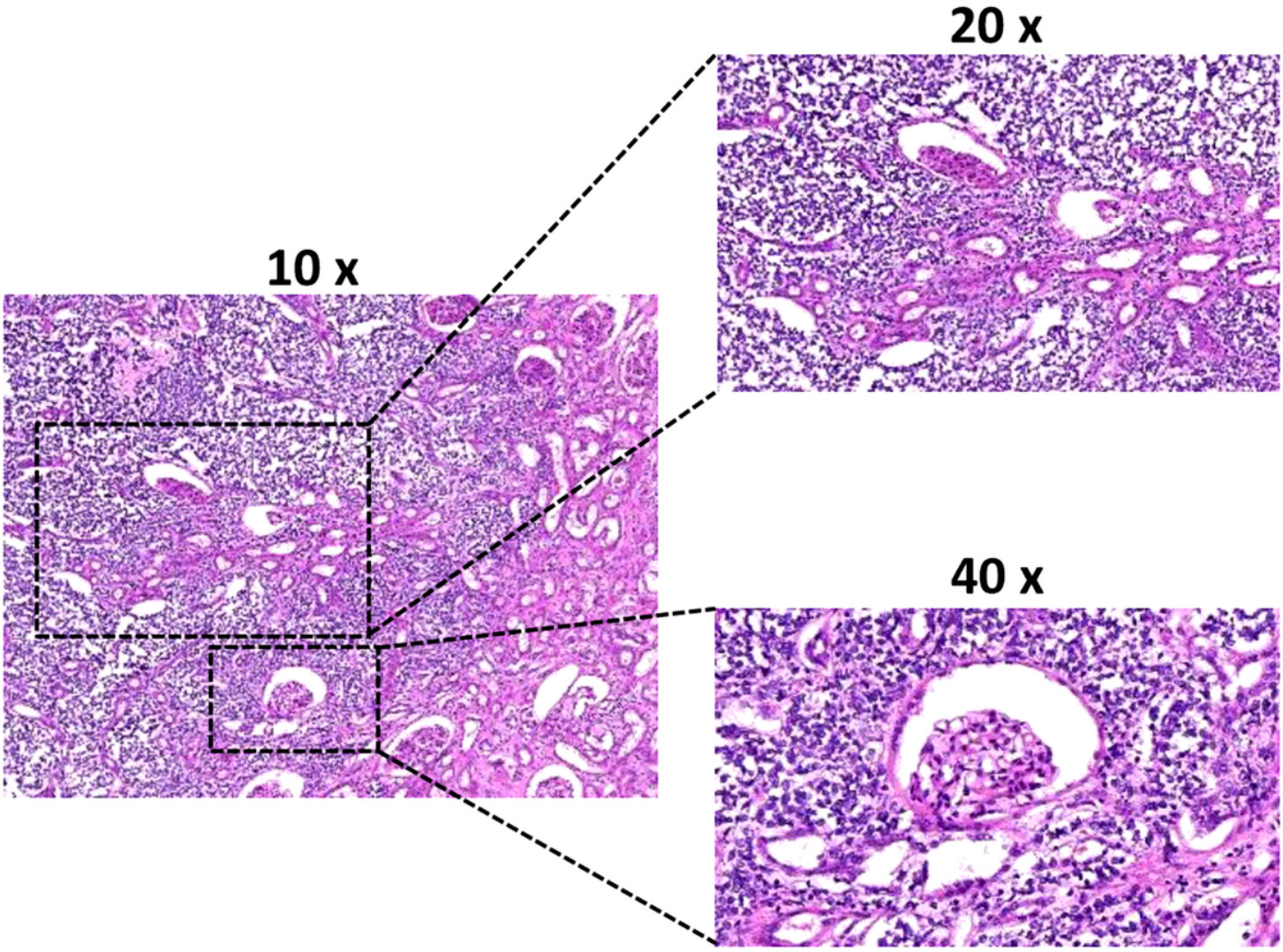

Figure 2

HE staining of tumor tissue.

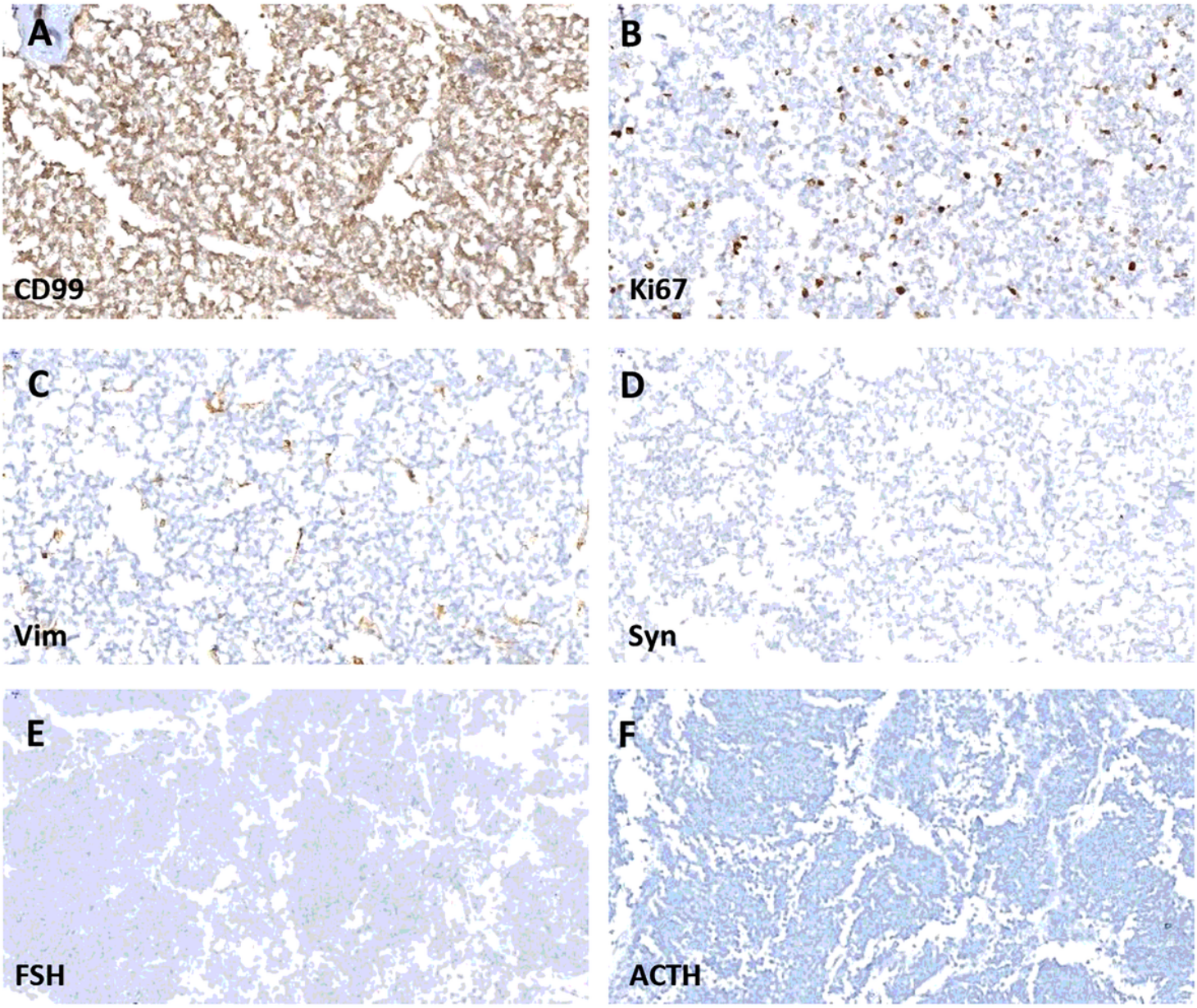

Figure 3

Immunohistochemical results in tumor tissue. A, CD99; B, Ki67; C, Vim; D, Syn; E, FSH; F, ACTH.

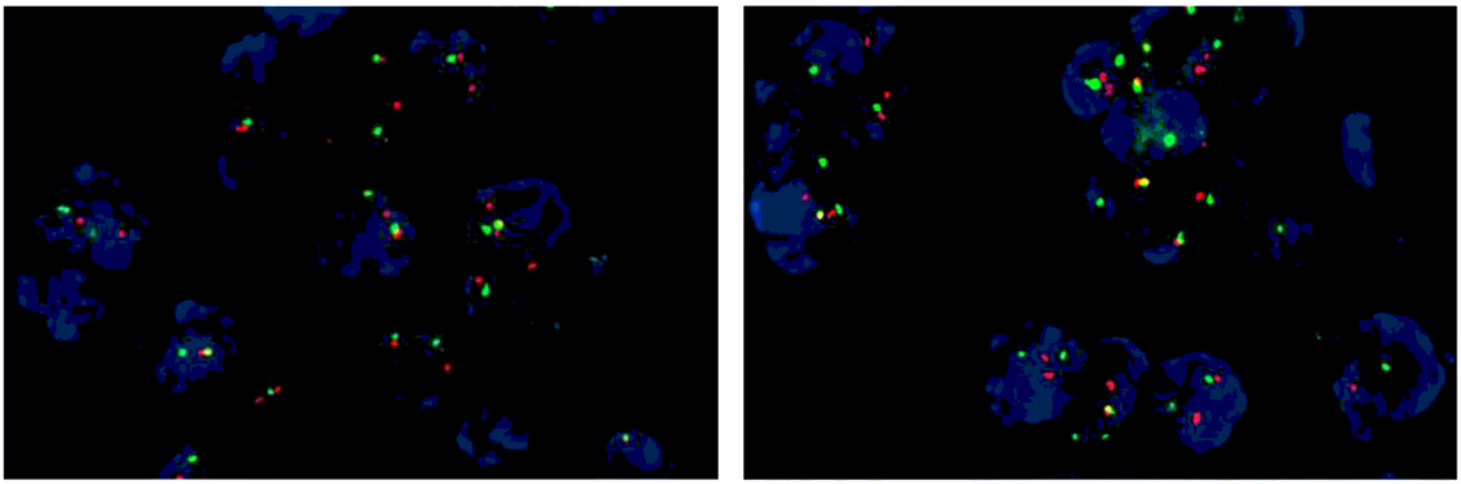

Figure 4

EWSRI gene fusion was detected by fluorescence in situ hybridization (FISH).

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