

## Chromophobe Renal Cell Carcinoma in Renal Allograft: Case Report

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**Abstract:** There is a great increase risk of developing renal cell carcinoma (RCC) in post-transplanted patients, mainly attributed to the immunosuppression. The majority of these RCC are developing in the native kidneys rather than the allograft of the renal transplant recipients, and the most common histological variant is clear cell carcinoma. Chromophobe renal cell carcinoma is a rare subtype of renal epithelial carcinoma with distinctive histological and immunohistochemical features and associated with good prognosis. Chromophobe renal cell carcinoma occurrence in allograft kidney in renal transplant recipients is extremely uncommon. One case of chromophobe renal cell carcinoma has been reported in 13.5-years-old boy who is a living-related kidney transplant recipient. We reported an exceptionally rare case of chromophobe renal cell carcinoma in allograft kidney in 52-years-old women, 15 years post living-unrelated renal transplant along with chronic hepatitis C infection. The tumor was discovered incidentally during routine ultrasound evaluation. The tumor revealed the typical histological and immunohistochemical features of chromophobe renal cell carcinoma.

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### 1.Introduction:

Developing primary malignancies is a well-established complication of immunosuppressive therapy in organ allograft recipients. Among these tumors, skin cancer and lymphoproliferative disorders are the most common malignancy (1, 2). Renal cell carcinoma (RCC) is the most common renal malignancy of adult who is a renal transplant recipient (3). The incidence of RCC in renal transplant recipients is 4.6% (4); 3.4% occurred in native kidneys and 0.5% in transplanted kidneys (5). The most common histopathological variant of RCC that occur in the transplanted kidney is the clear cell type followed by the papillary type. To the best of our knowledge Chromophobe RCC in the allografts kidney has been rarely reported in the literature. In a single series of de novo RCC in allografts, Ploussard *et al.* (6), found eleven cases of confirmed RCC in the renal allografts; five cases were papillary RCC, four cases were clear cell carcinoma, two cases were combined histology one papillary and clear cell, and the other papillary, clear cell and chromophobe cell carcinoma. In addition, one case of chromophobe RCC was reported by Greco *et al.*, in renal allograft in a 13.5-year-old boy (7). Here we report a rare case of chromophobe RCC in allograft in a 52-year-old female 15 years after living- unrelated renal transplant. We describe the radiological and histopathological findings.

### 2.Case Report:

A 52-year-old woman who was suffering from hypertension and chronic hepatitis C infection and had undergone living unrelated kidney transplant 15 years ago. In 1991, at the age of 30 during her 9<sup>th</sup> pregnancy, the patient developed high blood pressure and proteinuria, although she continued uneventful term pregnancy ended with spontaneous vaginal delivery. She continued to have the hypertension along with mild deterioration in her renal function, though she was complying with antihypertensive medications. Five years later, during her 10<sup>th</sup> pregnancy her renal function declined dramatically. However, she had unremarkable spontaneous vaginal delivery and bilateral tubal ligation was done for her. At that time she was diagnosed with end-stage renal failure and kept on irregular hemodialysis until two years later on 1998 at the age of 37 her condition worsened. She developed pericardial effusion, hyperkalemia and her creatinine was 1269  $\mu\text{mol/l}$  [60-105]. After her condition stabilized, pre-transplantation investigations showed that the patient has hepatitis C infection. Liver enzymes were within normal limits and liver biopsy showed grade 2 and stage 1, and she didn't receive any therapy for Hepatitis C infection. However, living-unrelated kidney transplantation was done, her condition improved, and she was under immunosuppressant maintenance therapy for 15 years. Throughout this period of time, ultrasound (U/S) was regularly done for her to assess her liver and kidney.

On July 2013, at age 52 years old, an allograft kidney mass was discovered incidentally during routine ultrasound check up, though she was free of symptoms and her renal function was mildly deteriorating. The ultrasound revealed a well-defined, echogenic, solid lesion in the renal allograft measuring 7.8 x 6.2 cm (Fig.1). Complementary computed tomography (CT) with contrast of the chest, abdomen, and pelvis was performed to assess the renal allograft and to evaluate for any evidence of metastasis. The graft kidney showed a well-defined, mid renal, heterogeneously enhanced solid lesion measuring 8.7 x 8.2 x 7.7cm. Both native kidneys showed features of end-stage renal disease. The liver showed fatty changes without any significant lesions. The remaining CT scan findings were within the normal limits. The US guidance Tru-Cut biopsy was obtained from the renal allograft and showed an epithelial neoplasm composed of sheets of large polygonal cells intersected by fibrovascular septa with limited tubules formation. The cells vary in size from small to large with abundant pale to pink granular cytoplasm, irregular "raisinoid" nuclei with binucleation and thick distinct cell membranes. The largest tumor cells tend to aggregate adjacent the fibrovascular septa. The tumor cells were positive for CK7, CD117, E-Cadherin, EMA and Galectin -3, but negative for vimentin and CD10. Hale's colloidal iron showed weak cytoplasmic positivity. According to these findings, the tumor was classified as Chromophobe renal cell carcinoma. A radical nephrectomy of the allograft was done. The patient tolerated the operation well with uneventful post-operative phase. The allograft nephrectomy specimen weighs 519 grams and the kidney measures 14x10x6 cm. It contained a large round well-circumscribed tumor measuring 8x7x7 cm at the center with golden yellow cut surface and no lymph nodes were resected (Fig.2). Microscopically, the tumor was consistent with chromophobe renal cell carcinoma with Fuhrman nuclear grade 3 and exhibited the same features as described earlier in the biopsy (Figs.3, 4). The tumor was confined to the kidney and no evidence of vascular invasion with clear vascular and ureteric margins. The renal parenchyma adjacent to the tumor shows few sclerosed glomeruli with chronic inflammation.

### 3. Discussion:

Nowadays, the best treatment choice for end-stage renal failure is renal transplantation, though it is associated with a well-established increased incidence of developing de novo cancer mainly attributed to the use of immunosuppressant. Among these cancers, the most frequent types are squamous cell carcinoma (lip, cervix, vulva, skin) and post-

transplant lymphoproliferative disorder according to the Cincinnati Transplant Tumor Registry and other reports (5, 8). It was reported that the primary RCC in renal transplant recipients accounts 4.6% of all malignancies in this subgroup, 90% in the native kidneys and 10% in the allograft (9, 10). Leveridge *et al.*, found in a retrospective study of a single center recipient population, the incidence of developing RCC in renal transplant recipients is more than 30 times than that of general population (11). Usually, RCC when raised in renal transplant patient commonly affect the native kidneys and few cases reported in the allograft (12,13). The most common histological variant of RCC in renal transplant recipients is the same as with general population, conventional clear cell type constitute the majority of the cases followed by papillary type and chromophobe type (14,15). Leveridge *et al.*, (11), observed the same findings in a retrospective analysis of 3568 renal transplant recipients, forty five renal tumors were diagnosed in 39 renal transplant patients, 37 of them in native kidneys and 8 in the allograft. Clear cell Carcinoma was the major histological type in native and allograft kidneys followed by papillary type. Moreover, one case was diagnosed as chromophobe RCC in native kidney. Ianhez *et al.*, Year (14), also found supporting results in a review that includes 1375 histories of renal transplant patients, in which 11 tumors were found in 10 patients, 10 tumors were in the native kidneys and 1 was in the allograft. Clear cell type carcinoma was the most common type in this study, it occurred in 6 cases, the papillary type in 4 cases and chromophobe in 1 case. The tumor in the allograft was papillary type. In another study, Ploussard *et al.*, (6) reported a follow-up cohort of 2396 renal transplant recipients, 17 de novo RCC in allografts of 12 patients. The biopsy confirmed RCC in 11 cases and papillary type was the most common, occurred in 5 cases, clear cell type in 4 cases and two cases were combined types, one of them was mixed papillary, clear cell and chromophobe type.

According to the literature, chromophobe renal cell carcinoma in renal allograft was rarely reported in renal transplant recipients. To best of our knowledge, Greco *et al.*, (7), reported an incidental finding of chromophobe renal cell carcinoma in 13.5 years who was a living-related kidney transplant patient. Here we present a very rare adult case of living-unrelated kidney transplant patient with chronic hepatitis C infection who was diagnosed with a renal allograft tumor in routine ultrasound. The tumor showed typical histopathological and immunohistochemical features of chromophobe RCC.

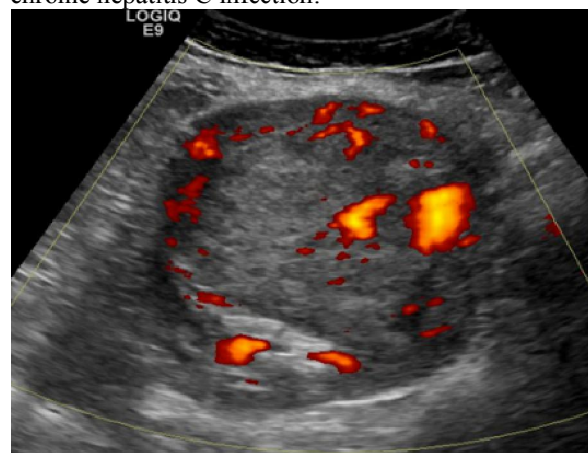
Chromophobe RCC was first described in 1985, (16) and it is derived from the intermediated cells between the distal and collecting tubules. It accounts for 4-6% of adult renal epithelium (18,19) and occur mainly in the 6<sup>th</sup> decade of life with similar incidence in men and women. However, its incidence in renal allograft of transplanted patient is extremely rare. This subtype is distinctive and histologically divided into three types: a classical variant (pale cells constitute more than 80% of tumor cells), an eosinophilic variant (eosinophilic cells constitute more than 80% of tumor cells), and mixed variant. One characteristic and distinguishing feature of chromophobe RCC is diffuse positivity of Hale's colloidal iron stain, but is not specific feature. As in our case, tumor cells were weakly stained. However, the characteristic immunophenotype panel of chromophobe RCC, the diffuse positivity of CK7 & CD117, was present in our case. It is suggested that CD10 and vimentin should be added in the panel to differentiate from other subtypes. It is believed that chromophobe RCC has a favorable prognosis and usually present in low stage. In this case, the tumor presented in low stage and confined to the kidney, as a result we are predicting a good prognosis for this tumor.

We presumed a case of chromophobe renal cell carcinoma that originated *de novo* in the renal allograft, after long interval, more than 10 years, between the times of transplantation and developing the cancer. In a large analytical study, Penn *et al.*, suggested (4) that the early occurrence of tumor in renal allograft is most likely pre-existed in renal parenchyma before transplantation. Ploussard *et al.*, (6), revealed in a cohort study, 13 years period was the mean time between the renal transplant and RCC. Implying that such a long interval and non-existence of early RCC were congruent with *de novo* RCC developing in allograft.

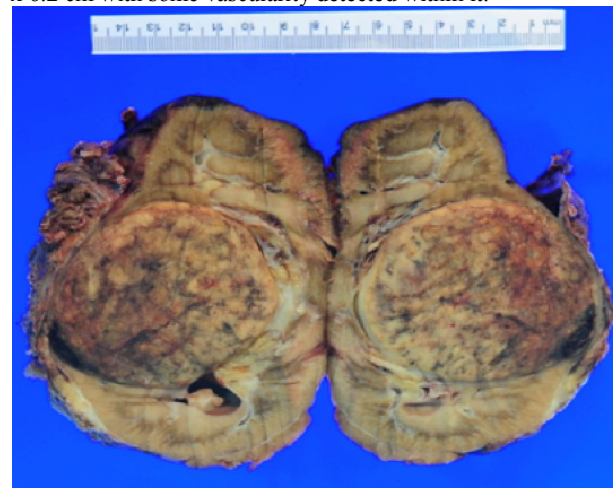
The risk factors for developing RCC in native kidneys in renal transplant recipients are relatively well-found such as the time spent on hemodialysis and acquired cystic kidney disease but is not well defined for developing *de novo* RCC in renal allograft (6). However, it is well-known that long term immunosuppression play a major role in developing cancer in a renal transplant recipient, and many of these cancers are infection-related. In view of our case and beside the long term use of immunosuppressant, the patient was harboring another risk factor that might contribute to the development of RCC which is chronic infection with Hepatitis C virus for more than 10 years and before she received kidney transplantation. Hepatitis C virus is well classified as oncogenic virus. Gorden *et al.*, (20), reported a large cohort study, suggested that chronic

hepatitis C infection increase the risk of developing RCC.

In summary, we described an extremely rare case with striking features of chromophobe renal cell carcinoma in allograft kidney of a renal transplant recipient, who happened to be chronically infected with hepatitis C virus. RCC is relatively common in the native kidneys of renal transplant patient and clear cell type is the main histological subtype but it's uncommonly develop in the allograft kidneys and very rare to be of chromophobe cell subtype. This tumor was discovered incidentally in our patient during routine ultrasound for liver assessment. Long-term screening protocols to detect malignancy are recommended for renal transplant recipients, especially for patient with long-standing kidney transplant and particularly in patient with associated chronic hepatitis C infection.

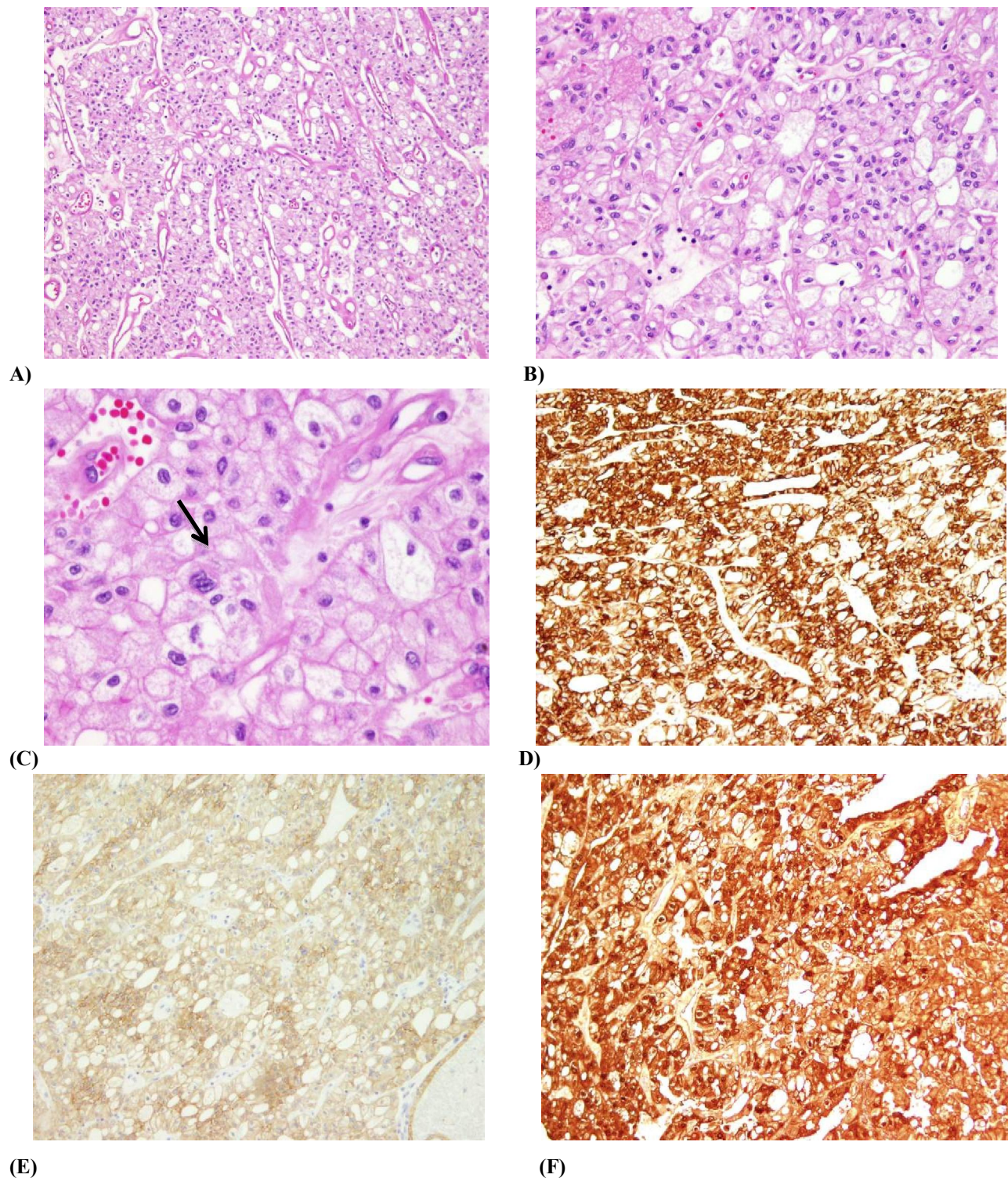


**Fig 1.** Ultrasound of the allograft kidney that shows large solid well-defined mid pole exophytic lesion measuring 7.8 x 6.2 cm with some vascularity detected within it.



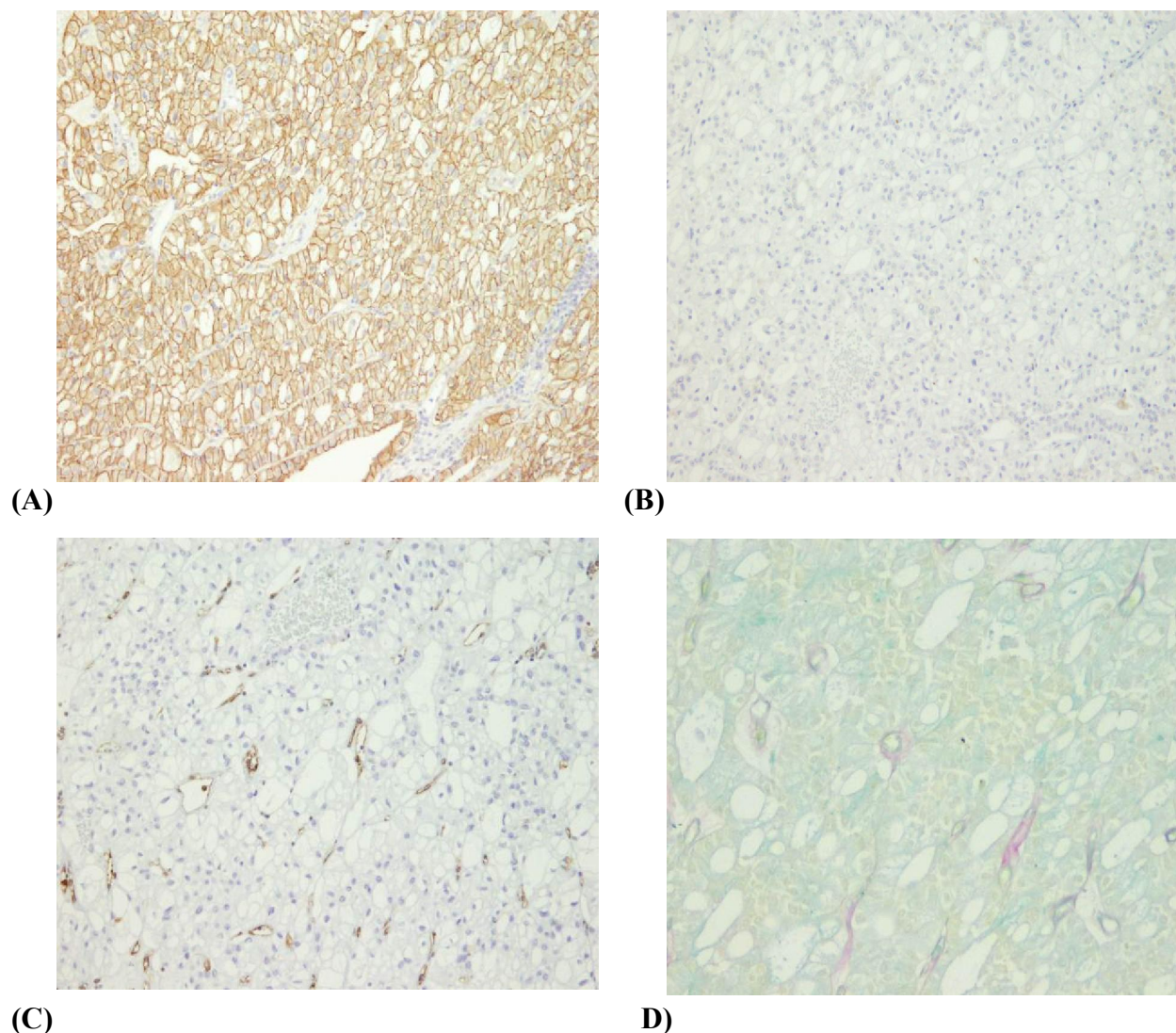
**Fig.2:** Surgically removed allograft kidney containing round large round well-circumscribed tumor measuring 8x7x7 cm at the center with golden yellow cut surface and multiple hemorrhagic foci.





**Fig. 3** Microscopic images of the Allograft renal lesion. A) The tumor is composed of large polygonal cells arranged in sheets and vague tubules with delicate microvascular septa (H&E; original magnification x 100). B) The tumor cells show variable eosinophilic to pale flocculent cytoplasm with distinct thick membrane. The large cells tend to be adjacent to the microvascular septa (H&E; original magnification x 200). C) The tumor nuclei are irregular, moderate in size with binucleation (arrow) (H&E; original magnification x 400). D) Tumor cells are positive for CK7 in a membranous pattern by means of immunohistochemistry (IMH) (Original magnification x 100). E) Tumor cells are positive for CD117 in a cytoplasmic pattern by means of IMH (Original magnification x 100). F) The tumor cells express Galactine 3 in a nuclear and cytoplasmic pattern (Original magnification x 100).





**Fig.4:** A) The tumor cells are expressing E-cadherin in a membranous pattern by mean of IMH ( original magnification x100). B) The tumor cells are negative for CD10 (original magnification x100). C) The tumor cells are negative for vimentin (original magnification x200). D) Hale Colloidal iron stains weakly the tumor cells (original magnification x200).

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