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**Are liver nested stromal epithelial** **tumors always low aggressive?**

Meletani T *et al*. Aggressive liver nested stromal epithelial tumor

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**Abstract**

Nested stromal-epithelial tumor (NSET) is a non-hepatocytic and non-biliary tumour of the liver consisting of nests of epithelial and spindled cells with associated myofibroblastic stroma and variable intra-lesional calcification and ossification, which represents a very rare and challenging disease. Most of the reported cases have been treated with surgery, obtaining a long survival outcome. Here we report the case of a 31 years-old Caucasian man who underwent surgery at our institution for a large, lobulated, multinodular mass of the right hemi-liver. The histological exam confirmed the diagnosis of NSET. After 6 mo from surgery, a liver recurrence was described and a chemo-embolization was performed. After a further disease progression, based on the correlation between the histological features of the disease and those of the hepatoblastoma, a similar chemotherapy regimen (with cisplatin and ifosfamide/mesna chemotherapy, omitting doxorubicin due to liver impairment) was administered. However, infectious of the biliary catheter required a dose modification of the treatment. No benefit was noted and a progression of disease was radiologically assessed after only four cycles. The worsening of the clinical status prevented further treatments, and the patient died few months later. This case report documents how the NSET might have an aggressive and a not preventable behavior. No chemotherapy schedules with a proved efficacy are available, and new data are needed to shed light on this rare neoplasm.

**Key words:** Nested stromal epithelial tumor; Liver; Rare; Chemotherapy; Aggressive; Metastatic

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**Core tip:** Nested stromal-epithelial tumor (NSET) of the liver is a very rare type of cancer, few cases have been reported in the world. Most of the literature described a low tendency of relapse, the majority of the reported cases have been treated with surgery, obtaining a long survival outcome. Our patient developed a more aggressive disease, which relapsed soon after surgery, and progressed after first line chemotherapy. We aimed to update the literature about NEST; especially in patients with either metastatic or recurrent disease, for whom no standard treatment is now available.

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**INTRODUCTION**

Nested stromal-epithelial tumor (NSET) of the liver is a very rare type of cancer[1] with few cases diagnosed worldwide. It usually, affects young people with a age range from 1 to 34 years[2] and no sex preference. A Cushing syndrome is often the presenting symptom of this neoplasm[2-4].

The right liver lobe is mostly involved, with a well-circumscribed, large mass characterized by calcification at the computer tomography (CT scan) imaging[1].Histological features, include circumscribed nests and islands of bland-appearing spindled to focally epithelioid cells, surrounded by a cellular desmoplastic stroma, with non-hepatocytic and non-biliary duct characteristics[5].

Here we present a clinical case of a patient with NSET, with the aim of sharing our experience.

**CASE REPORT**

***Diagnosis and surgery***

In March 2015, a 31 years-old Caucasian man presented at Surgery Department complaining for weight loss (approximately 5% of body weight during the previous 2 mo) and abdominal pain. His father underwent liver resection for unspecified liver neoplasm 12 years before and no other significant family history of illness or tumor emerged. The patient had no history of alcohol abuse or hepatitis; he had been followed for arterial hypertension and treated with Ramipril and Nebivolol.

Physical examination revealed a palpable large abdominal mass in the right upper quadrant with no evidence of ascites or splenomegaly. Laboratory findings revealed a high level of gamma-glutamiltransferase (349 U/L) and a mild leukocytosis (13.8 × 103 cells/mm3); serology for hepatitis B, C, autoimmune hepatitis and human immunodeficiency virus was negative. Serum alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 were within in normal range.

The CT scan showed a large, lobulated, multinodular mass (22 cm × 13 cm × 25 cm) with few round calcifications mainly in the central part, involving entirely the right hemi-liver, partially the Couinaud’s segment 4, and the caudate lobe. After administration of iodinated contrast material, the tumor showed not homogeneous, early enhancement in the arterial phase, with subsequent washout in the portal and delayed phases. The CT images also demonstrated an extensive infiltration of the right portal branch and of the right and middle hepatic veins with a consequent spontaneous hypertrophy of the left lobe (Figure 1).

The surgical procedure consisting in a virtual resection was planned[6]. The quantitative analysis of CT images showed a Total Liver Volume of 5797 cm3, a Tumor Volume of 3879 cm3 with ahypertrophic remnant left liver lobe (Couinaud’s segments II and III) of 1329 cm3. The Future Liver Remnant thus resulted of 69%, markedly over the safe cut-off[6]. Basing on these radiological findings, a right trisectionectomy extended to the caudate lobe was proposed.

On laparotomy, careful exploration of the abdominal cavity ruled out no extrahepatic manifestations; intraoperative ultrasound revealed another 2 cm nodule in segment II. The remaining left lobe did not show any histological alterations at intraoperative biopsy. Hepatoduodenal ligament was dissected to isolate and ligate the right hepatic artery, portal vein and bile duct as well as the biliary and vascular elements for segment IV and I (Figure 2). After transection of the right portal vein, that appeared infiltrated by the tumor, the hepatic parenchyma was dissected between segments II/III and segment IV by using Cavitron ultrasonic surgical aspirator (CUSA) andargon diathermy. Afterwards, the nodule at the hepatic segment II was treated by radiofrequency ablation.

Postoperative course was uneventful, except for a 4.5 cm fluid collection on the cutting surface of the liver that was successfully treated by percutaneous drainage. The patient was discharged on postoperative day 21 with a completely preserved liver function.

***Pathological features***

**Gross appearance:** The right hepatic lobe was almost entirely occupied by a multinodular mass with homogeneous whitish cut surface, partially necrotic and with calcifications. The lesion had a greatest diameter of 19 cm and was 0.5 mm far from the surgical margin (Figure 3).

**Microscopic and immunohistochemical features:** Histologically, the neoplasm showed an organoid arranged tumor of well-defined nests of epithelioid and spindle cells with focal necrosis, surrounded by hypercellular stroma with areas of osseous metaplasia and calcifications. The cellular nests were oval, elongate, irregular with rounded edges. The epithelioid part of the tumor was composed by monomorfous polygonal and spindle-shaped cells, round to oval nuclei with finely stippled cromatin and unappearance nucleoli. The cytoplasm was eosinophilic in most areas, with few cells containing clear cytoplasm (Figure 4). The cellular nests showed positive staining for markers of epithelial differentiation positive for CAM 5.2, AE1/AE3, EMA (focal), β-catenin (both membrane and nuclear), WT1 (both membrane and cytoplasmatic), GPC3 (focally cytoplasmatic) and CD56 (diffuse) and negativity for hepatocyte antigen EpPar1 (hepatocyte paraffin 1), CK7, CK19, CD34, CD99, cromogranin and desmin. The calcifications were most commonly within or adjacent to cellular nests. The mitotic index was 10 mitotes/10 high power field (40 × objective). The stroma surrounding the cellular nests showed a myofibroblastic nature, with spindled cells with long tapered cytoplasmic processes, positive staining for smooth muscle actin (ACTML) and negative for citokeratins and EpPar1. Bile ducts entrapped in the fibrous stroma were normal and were highlighted by CK7 and CK19 immunohistochemical stains (Figure 5). The neoplastic cells infiltrated the surrounding hepatic parenchyma and peri-hepatic soft tissue. Vascular invasion of a portal vein branch was demonstrated.

**Differential diagnosis:** The differential diagnosis of a biphasic tumor, with a spindled and epithelioid component, with variable calcifications and osseous metaplasia includes in the first instance synovial sarcoma, mixed epithelial and mesenchymal hepatoblastoma and calcifying nested stromal-epithelial tumor. Desmoplastic small round cell tumor (DSRCT) is also a diagnostic consideration in a young patient. In addition should be considered the possibility of a sarcomatous variants of hepatocellular carcinoma or cholangiocarcinoma. However, these tumors lack the nested, organoid architecture of NSET, typically showing a greater cytological atypia.

Areas predominantly composed of epithelioid nests may resemble islands of fetal hepatoblastoma cells. However, the neoplasm in this report lacked the fetal and/or embryonic hepatoid features of the epithelial component of mixed hepatoblastoma, and neither the spindled nor the epithelioid lesional cells stained with the hepatocyte specific tissue stain EpPar1.

The overall histology and immunohistochemical features supported the diagnosis of NSET, a very rare tumor defined as a non-hepatocytic and non-biliary tumour of the liver consisting of nests of epithelial and spindled cells with associated myofibroblastic stroma and variable intralesional calcification and ossification[4,7,8].

For a comprehensive report, molecular analysis was performed. Reverse transcriptase-polymerase chain reactions (RT-PCR) for SYT-SSX and EWS-WT1 were negative in our case. Such findings, combined with the histological appearance, allowed us to rule out the hypothesis of synovial sarcoma and DSRCT, respectively.

***Relapse***

In September 2015 the patient underwent a CT scan which showed several liver lesions (maximum diameter of 17 mm) and also a positron emission tomography (PET) that documented a pre-sacral nodule (SUV = 5).

After discussion within the Multidisciplinary Tumor Board (MTB), since surgery was judged not feasible, a liver chemo-embolization (DCBeads + doxorubin) was performed. Albeit the arteriography showed a higher number of the lesions, only five nodules were treated with the chemoembolization.

Due to an increase of the gamma- glutamiltransferase (944 U/L) no further treatment was practicable.

In November 2015, a re-assessment with a CT scan showed a local progression and an increased number of abdominal lymphoadenopathies. Hyperbilirubinemy (10.2 mg/dl) was also observed with a dilatation of the intrahepatic biliary duct. Therefore, a trans-cutaneous biliary catheter was positioned an consequent improvement of the hepatic and biliary function.

Then the patient was revaluated within the MTB and we hypothesized regimen with Ifosfamide/Mesna, Platin and Anthracycline according to IPA schedule.

Due to the correlation of the histological features of the disease with the hepatoblastoma as described in literature[9–12], Four courses of Cisplatin (100 mg/m2) and Ifosfamide/Mesna (3 g/mq) were administered, omitting doxorubicin because of the liver impairment.

Anyway, infectious of the biliary catheter, with fever and abdominal pain, affected the treatment, and required both antibiotics and a dose modification of the chemotherapy schedula. In fact, Cisplatin alone was administered in the second course and Ifosfamide/Mesna was added again from the third one, reducing by 50% of its total dose. The patient received a total of four cycles of chemotherapy.

In April 2016, a restaging CT scan showed a progressive disease, represented by an increase of the hepatic lesion (5 cm *vs* 2.4 cm) and of the pre-sacral nodule (2.6 cm *vs* 1.7 cm). Ascites was also documented. (Figure 6)

Unfortunately, the worsening of the clinical status, the risen of the total bilirubin up to 27.4 mg/dl and alterations of sodium and potassium, prevented the further administration of chemotherapy and the patient died in June 2016.

**DISCUSSION**

Nested stromal-epithelial tumors are a very rare type of cancer, and few data about their treatment are available.

As far as we know, there are no predisposing factors increasing the risk of occurrence of this rare type of tumor. In literature was described a few cases of NEST associated with Cushing syndrome at diagnosis. In this cases after excision of the tumors the Cushing syndrome was abated, but the correlation remain unknown[2-4].

Considering the low tendency of relapse, the majority of the reported cases have been treated with surgery, obtaining a long survival outcome (up to a complete response) in most of them[2,12].

Liver transplantation is a further treatment that should be taken in account in patients with unresectable and not extrahepatic disease, although not as a first choice[1,13]. Homman *et al*[13] treated a 19 years old patient who underwent liver surgery for a NSET and developed liver metastasis few years later with a liver transplantation, achieving a 37 mo of OS.

Our patient relapsed within 6 months after surgery, with several focal lesions into the residual liver, showing an aggressive and unusual behavior of the disease. Necrosis, high mitotic rate, invasion of the surrounding parenchyma and vascular invasion are the features that might explain the malignant potential and so the aggressive behavior of this rare neoplasm. Furthermore, a liver transplantation was not performed because of the presence of the extrahepatic pre-sacral nodule.

Consequently, chemotherapy seemed to be the only feasible therapeutic approach, although no guidelines, prognostic or predictive factors are currently known to choose the most appropriated treatment.

The analogies between NEST tumors and hepatoblastoma led us to use a hepatoblastoma chemotherapy protocol to treat our patient. This decision was also supported by the literature. In fact cases of both recurred and metastatic disease have been treated with a good outcome[12]. Among the others a 3-year old child was treated both before and after resection, achieving a minimal shrinkage of the tumour[4]. Other two patients, of about 14 and 2 years old, were treated after surgery with the same chemotherapy protocol, with a disease free survival of 90 and 84 mo respectively[1]. It should be noted that all these cases were younger than our patient.

Nevertheless, our patient developed a more aggressive disease with a worse prognosis compared to the other known case reports known, and also several issues prevented a good compliance to the treatment. No tumor shrinkage was noted, but a progression of the disease in both liver and pre-sacral sites.

Other cases in literature had a poor prognosis[1,14], with overall survival (OS) around 37-40 mo, which was anyway better than our patient outcome (OS 15 mo), probably because they underwent liver transplantation.

In conclusion sharing our experience, we aimed to knowledge the literature about NEST; especially in patients with either metastatic or recurrent disease, when a chemotherapeutic rather than a surgical approach is requested and where prognostic and predictive factors are not still available.

**COMMENTS**

***Case characteristics***

A 31 years-old Caucasian man who presented at our institution for a large, lobulated, multinodular mass of the right hemi-liver.

***Clinical diagnosis***

Distended abdomen with diffuse tenderness, palpable large abdominal mass in the right upper quadrant with no evidence of ascites or splenomegaly.

***Differential diagnosis***

Hepatocellular carcinoma, metastatic adenocarcinoma, cirrhosis, hepatoblastoma.

***Laboratory diagnosis***

Increased of gamma-glutamiltransferase (349 U/L) and a mild leukocytosis (13.8 × 103 cells/mm3); serology for hepatitis B, C, autoimmune hepatitis and human immunodeficiency virus was negative. Serum alpha-fetoprotein, carcinoembryonic antigen and CA 19-9 were within in normal range.

***Imaging diagnosis***

The CT scan showed a large, lobulated, multinodular mass (22 cm × 13 cm × 25 cm) with few round calcifications mainly in the central part, involving entirely the right hemi-liver, partially the Couinaud’s segment 4, and the caudate lobe. The CT images also demonstrated an extensive infiltration of the right portal branch and of the right and middle hepatic veins with a consequent spontaneous hypertrophy of the left lobe.

***Pathological diagnosis***

The histological exam confirmed the diagnosis of nested stromal-epithelial tumor (NSET).

***Treatment***

The first approach was surgery. After relapse, four courses of cisplatin (100 mg/m2) and ifosfamide/mesna (3 g/mq) were administered, omitting doxorubicin because of the liver impairment.

***Related reports***

NSET of the liver is a very rare type of cancer which affects young people without sex preference. A Cushing syndrome is often the presenting symptom of this neoplasm.

***Term explanation***

NSET is usually a large hepatic lesion, partially necrotic and with calcifications. At the histology, it appears as well-defined nests of epithelioid and spindle cells with focal necrosis, surrounded by hypercellular stroma.

***Experiences and lessons***

This entity is usually associated with a good prognosis after surgery. Nevertheless, our patient prognosis was poor, the disease showed an aggressive behavior. No standard therapy is approved for the metastatic disease.

***Peer-review***

This case report showed the uncommon situation of a patient with a metastatic NSET, and the chemotherapy administered which had provided no benefit. The authors present very precisely the case of very rare type of liver cancer which have very aggressive form and progressed after surgery and first line chemotherapy.

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**Figure 1** **computer tomography examination and virtual resection.** a: pre-contrast acquisition, axial image cranial to the hilar plane showing a large, hypo-attenuating lobulated lesion involving the right hemiliver and part of the segment 4. White circle: calcification within the neoplastic lesion. B and c: axial images across the hilar plane during arterial (b) and portal (C) phase. Then neoplastic, lobulated lesion shows early arterial enhancement resulting hypo-attenuating during the portal phase. The right portal branch is not visible due to neoplastic infiltration (white arrows). D-f: virtual resection, volume renderings of CT images. D: total liver volume; the not homogenous red color of the right hemiliver corresponds to the lesion (black arrows); E: tumor lesion; F: future remnant liver corresponding to segments 2 and 3.



**Figure 2 Intra-operatory images and tumoral tissue.**



**Figure 3 Grossly, right hepatic lobe was almost entirely occupied by a well circumscribed multinodular mass with homogeneous whitish cut surface with calcification areas.** In detail, macroscopic neoplastic vascular invasion of a portal vein branch.



**Figure 4 Tumor showed organoid appearance with well-demarcated nests in a myofibroblastic stroma (A).** B: Areas of osseous metaplasia and calcifications; C: Epithelioid and spindle cellular nests with bile ducts entrapped in fibrous stroma; D: Epithelioid and spindle-shape cells with eosinophilic and clear cytoplasm.



**Figure 5 Immunohistochemical stains showed neoplasm negativity for hepatocyte paraffin 1 (EpPar1) (counterstained normal liver parenchima), negativity for CK7 (highlighted entrapped bile ducts between the tumor cell), stromal positivity for ACML and positivity for β-catenin (both membrane and nuclear).**



**Figure 6 Computer tomography scan**. A: CT scan performed in November 2015 showed sacral lesion; B: CT scan performed in April 2016 showed increase of sacral lesion; C: CT scan performed in November 2015 showed liver lesions; D: CT scan performed in April 2016 showed increase of liver lesions. CT: computer tomography.