Abstract
Solitary fibrous tumors (SFTs) are rare soft-tissue tumors that often occur in body cavities, especially the pleural space. A subset of SFTs is histologically malignant and tends to metastasize; rarely, they may induce paraneoplastic syndromes. Doege–Potter syndrome is paraneoplastic hypoglycemia induced by oversecretion of unprocessed insulin-growth factor-2. While localized SFTs are treated mainly by surgery, the standard therapy for metastatic SFTs is lacking. Here, we present a case with metastatic malignant SFT and Doege–Potter syndrome, which was treated initially by dacarbazine and bevacizumab with a period of good clinical response.

Keywords: Dacarbazine, Doege–Potter syndrome, malignant solitary fibrous tumor, paraneoplastic syndrome

INTRODUCTION
Solitary fibrous tumors (SFTs) are rare soft-tissue tumors with preferential sites subjacent to serous membranes such as the pleura and peritoneum, where they have been postulated to arise from submesothelial mesenchymal cells. SFTs are mostly intrathoracic tumors, while recent evidence suggests that extrathoracic SFTs are as prevalent and lead to a similar clinical outcomes. Another soft-tissue neoplastic nomenclature, hemangiopericytoma (HPC), is now considered to be the same disease entity as SFTs because of many shared pathologic features and the presence of unique NAB2-STAT6 fusion gene. Although SFTs tend to be indolent, malignant SFTs (MSFTs) are more aggressive. MSFTs tend to be larger, present with vascular invasion, metastasize, and more often manifest with paraneoplastic syndrome. The definition of MSFT remains controversial, although the proposed criteria for MSFT include high cellularity, increased mitotic activity, nuclear pleomorphism, and the presence of hemorrhage or necrosis. The cornerstone of treatment for MSFTs is surgery, however there is still no consensus for the management of inoperable MSFTs. Here, we present a case of metastatic MSFT complicated with paraneoplastic hypoglycemia (Doege–Potter syndrome) that was controlled after systemic therapy.

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**Case Report**

In February 2019, a 44-year-old male was sent to our emergency department with altered consciousness, cold sweating, and hand tremor. Hypoglycemia was noted (fingertip blood sugar: 45 mg/dL; normal range: 70–140 mg/dL before meals) at the initial evaluation, and his symptoms were relieved soon after the intravenous (IV) administration of dextrose. He reported several similar episodes occurring for 1 month, especially between meals. He also reported thirst, polyuria, and unexpected weight gain from 68 to 72 kg in the past 3 months. A physical examination revealed hepatomegaly (a liver margin 6 cm below the xyphoid process), and mild tenderness over his upper abdomen. Initial laboratory data were unremarkable. After stabilization, he was admitted to our endocrinology ward for further investigation and treatment.

Spontaneous hypoglycemia (blood glucose: 25 mg/dL) was confirmed with a 72-h fasting test. His serum cortisol and adrenocorticotropic hormone (ACTH) levels were within normal range (cortisol: 17.7 µg/dL, normal range 3.7–19.4 µg/dL; ACTH: 27.0 pg/ml, normal range: 7.4–57.3 pg/ml). However, his serum C-peptide and serum insulin levels were extremely low (C-peptide: 0.05 ng/ml, normal range 0.78–5.19 ng/ml; insulin: <1 µU/mL, normal range < 28.8 µU/mL). According to these data, adrenal insufficiency or insulinoma was less likely. The tentative diagnosis was nonislet cell tumor hypoglycemia, a situation often induced by large mesenchymal or epithelial tumors mediated by the oversecretion of several hypoglycemic hormones.

Contrast-enhanced computer tomography (CT) of the chest, abdomen, and pelvis showed heterogeneously enhanced tumors in both lobes of the liver, the largest being 13.5 cm in the right lobe [Figure 1a]. Other findings included bilateral kidney tumors (up to 14.9 cm in the left kidney upper pole), mixed sclerotic and osteolytic lesions in the L4 and L5 spine and right iliac bones, and multiple lung nodules [Figure 1b]. A CT-guided liver biopsy was arranged, and the pathology revealed a spindle cell sarcoma with a rich vasculature [Figure 2a], which in conjunction with diffuse STAT6 nuclear staining [Figure 2b] was highly suggestive of MSFT. Therefore, given that paraneoplastic hypoglycemia is well-known to be induced by SFTs, i.e., Doege–Potter syndrome, the hypoglycemia in the current case probably represented this paraneoplastic syndrome. Doege–Potter syndrome results from tumor-related oversecretion of unprocessed insulin-like growth factor II (big IGF-II). We did not check serum IGF-1, IGF-2, or big IGF-2 since these examinations were not available at our institution, but we had excluded most of the other probabilities. Overall, a metastatic MSFT complicated with paraneoplastic Doege–Potter syndrome was diagnosed.

With regard to his medical history, he had been diagnosed with an intra-abdominal diffuse large B cell lymphoma (DLBCL) at another hospital 9 years before this admission. After eight cycles of a standard regimen of R-CHOP (each cycle: rituximab 700 mg, cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 2 mg, and prednisolone 25 mg QID), complete remission was achieved. During the initial lymphoma staging, an enhanced meningeal-based nodule at the left parasagittal frontal lobe was revealed by brain magnetic resonance imaging (MRI) [Figure 3a]. A meningioma was diagnosed clinically, and close monitoring was recommended. However, the tumor enlarged gradually in the next few years and resulted in right side weakness in May 2014. It was then partially resected by a neurosurgeon, and the pathology examination reported an atypical meningioma. Adjuvant radiation therapy (60 Gy in 33 fractions) was done, however residual tumor was still noted in follow-up brain MRI, and he received further surgery in 2015. Afterward, his weakness resolved and he regularly visited a neurosurgeon. A recurrent meningeal tumor was noted on MRI in July 2018, 6 months before this admission [Figure 3b]. To clarify the relationship between this disease and his MSFT, we also reviewed the pathology slides of his previously resected meningeal tumor. We found that the meningeal tumor had pathohistological characteristics similar to those of his liver MSFT [Figure 4a] and was later confirmed to also show diffuse STAT6 nuclear staining [Figure 4b]. It is likely that his meningeal tumor was a MSFT which had become metastatic with paraneoplastic hypoglycemia.

During this admission for hypoglycemia, continuous IV dextrose infusion was required to prevent symptomatic events.
Diarrhea, poor oral intake, and subsequent poor performance further complicated his condition. A treatment plan was promptly discussed. Considering the cumulative heart toxicity, we decided to avoid further anthracycline usage. Other potentially efficacious chemotherapy included ifosfamide and dacarbazine. The oral multiple kinase inhibitor pazopanib was another choice for treatment, however the possible side effects such as diarrhea were a concern because of his ongoing diarrhea. We chose dacarbazine as the first-line systemic therapy, with a dose of 1000 mg/m² over 5 consecutive days, and no further hypoglycemic episodes occurred after the 1st day of treatment [Figure 5a]. On day 8 of treatment, fixed-dose bevacizumab 300 mg was administered for better tumor control. IV dextrose was stopped on day 10, and he was discharged on day 12 in a stable condition.

During the outpatient department follow-up, we consulted a general surgeon after his general condition improved, and surgery was arranged. Another cycle of bevacizumab plus dacarbazine was given on day 21. However, a hypoglycemic episode developed again on day 30, before surgery could be done. Oral cyclophosphamide 50 mg BID was added, but he could not tolerate treatment due to side effects such as fatigue. His abdominal distension deteriorated and further compromised his oral intake. He was then admitted and received the third dose of dacarbazine on day 51, and these symptoms subsequently improved slightly.

Another episode of altered consciousness developed on day 82 after the diagnosis. He was sent to our emergency department with hypoglycemia noted again (fingertip blood sugar: 16 mg/dL). Contrast-enhanced CT of the chest, abdomen, and pelvis revealed progression of the intra-abdominal and bilateral lung metastases. He was admitted and we gave him pazopanib 400 mg QD from day 82, however his hypoglycemia persisted. As a salvage treatment, gemcitabine 600 mg/m² plus paclitaxel 80 mg/m² for two cycles were given, with only a limited effect. Hypoglycemia occurred intermittently despite total parental nutrition support [Figure 5b]. As his condition deteriorated, he signed do-not-resuscitate orders, and he died from the progressive disease on day 135.

**Figure 3:** Serial brain MRI scans of this patient in 2014 and 2018, respectively. (a) Coronary image of a brain MRI scan in 2014 revealed an enhanced, parasagittal frontal lobe, dura-based tumor, compatible with a meningioma. (b) A coronary image of a brain MRI scan in 2018 revealed a 2.4-cm recurrent lobulated heterogenous tumor at the left parasagittal convexity (arrowhead). Parenchymal loss at left frontoparietal lobes was also noted.

**Figure 4:** The pathohistological findings of the patient's meningeal tumor. (a) Hematoxylin and eosin staining, ×100. Note the atypical spindle cells with nuclear polymorphism, staghorn-like vessels, and interlacing collagen, somewhat similar to Figure 2a. (b) Tumor cells were diffusely positive for STAT-6, ×100

**Discussion**

Our patient had a parasagittal frontal lobe dural tumor resected in 2014, and this dural tumor was pathologically similar to his hepatic MSFT. Importantly, STAT-6 was positive in both specimens. Therefore, a diagnosis of meningeal MSFT with distant metastases was confirmed. Central nervous system (CNS) SFTs are rare, dura-based tumors. They comprise two phenotypes: the SFT phenotype with similar characteristics to other extracranial SFTs (Grade I) and the HPC phenotype with more aggressive behavior and a tendency to recur and metastasize extracranially (Grades II and III), therefore considered to be a malignant form of meningeal SFTs. Unlike other primary CNS tumors, MSFTs have a high risk of extracranial metastasis. In a series of 39 cases, meningeal MSFTs/HPCs developed extracranial metastasis in 26% of patients. Thorough examinations for extracranial metastasis are warranted in patients with CNS MSFTs.

Paraneoplastic syndromes such as hypoglycemia (Doege–Potter syndrome) have been reported in about 2%–4% of MSFT patients. The mechanism of hypoglycemia has been proposed to be tumor-related oversecretion of incompletely processed precursor big-IGF-II. This protein passes the capillary membrane more easily and increases an insulin-like effect at the tissue level. The treatment of Doege–Potter syndrome is IV glucose-containing fluid infusion and managing underlying malignancy. Retrospective studies have reported that complete resection of the tumor helps control the paraneoplastic syndrome. In our case, the metastatic tumors were initially borderline resectable. However, we had to postpone surgery due to aggressive hypoglycemia and initiated chemotherapy first to relieve his symptoms.

There is currently no standard treatment of metastatic MSFTs due to their rarity and lack of randomized controlled trials. An Italian retrospective study including 17 MSFT patients demonstrated mild antitumor activity with an anthracycline-based regimen (response rate: 11%). A combination with ifosfamide or dacarbazine was used in some cases with a response, and the median progression-free survival of this cohort was 4.6 months. Another retrospective study from the MD Anderson Cancer Center found no responders...
with anthracycline-based regimens.\cite{12} Nevertheless, the same study team presented another retrospective cohort treated by a combination of temozolomide plus bevacizumab, with a substantial response rate of 79% according to the Choi criteria.\cite{10} The rich vascular characteristics of MSFTs support the rationale of vascular endothelial growth factor blockade. Several multitargeted kinase inhibitors have been investigated in phase 2 studies, with only limited effects on SFTs.\cite{13} Pazopanib has been shown to demonstrate antitumor activity against malignant and dedifferentiated SFTs, with a response rate of 51% according to the Choi criteria (6% by RECIST 1.1).\cite{17} Whether the higher Choi response rate can translate into survival benefit remains unknown.

As for our patient, the accumulated doxorubicin dose for DLBCL treatment precluded further anthracycline use. In addition, he could not afford temozolomide, which was not reimbursed by the National Health Insurance system. As a result, we chose dacarbazine plus bevacizumab according to the aforementioned clinical evidence.

The patient’s hypoglycemia was relieved from day 1, and he was discharged smoothly on day 12 without further IV dextrose support. It is possible that IV steroids as a premedication also helped stabilize his serum glucose. Nevertheless, his baseline serum cortisol and ACTH levels did not support the diagnosis of adrenal insufficiency, and the clinical benefit of chemotherapy persisted after he discontinued steroids on day 9 [Figure 5a]. These facts support the efficacy of systemic therapy in controlling paraneoplastic hypoglycemia. In the second-line setting, neither pazopanib nor gemcitabine plus paclitaxel provided significant benefits as salvage treatment for this patient.

Figure 5: Line chart of fingertip blood sugar during the two admission periods. (a) The trends of average and lowest blood sugar of this patient during the first admission. Note that the difference between two values decreased from treatment day 1, indicating a lower frequency of hypoglycemia after the administration of dacarbazine. This clinical benefit persisted even without steroid use after day 9. The relatively lower sugar level on day 11 was considered to be related to the discontinuation of IV dextrose infusion. (B: bevacizumab 200 mg IV infusion 30 min, D10: dextrose 10% IV continuous infusion, DTIC: dacarbazine 200 mg/m² IV infusion 30 min/day in 5 subsequent days). (b) The trends of average and lowest blood sugar of this patient during the last admission. Despite pazopanib use, there were still many hypoglycemic events before day 129. After gemcitabine and paclitaxel infusion, along with TPN support, his blood sugar improved slightly and the effect lasted for several days. (G: gemcitabine 600 mg/m² IV infusion 30 min, P: paclitaxel 80 mg/m² IV infusion 60 min, PPN: peripheral parenteral nutrition, glucose 75 g/L; TPN: total parenteral nutrition, glucose 240 g/L).

Although this strategy has not been proven to be effective in vivo, this result suggests the possibility of using IGF inhibitors to treat paraneoplastic hypoglycemia.

In conclusion, we demonstrated a case of meningeal MSFT with extracranial metastases and accompanying Doege–Potter syndrome. Dacarbazine and bevacizumab adequately controlled the paraneoplastic hypoglycemia for a period of several months, even before a radiologic response was documented. Nevertheless, the short duration of response is consistent with previous reports.\cite{6,12} This may have been due to acquired chemotherapy resistance. Further investigations of more potent and durable systemic therapies for inoperable MSFTs are warranted.

**Ethical approval**

This study is approved by the IRB of National Taiwan University Hospital (IRB approval number: 202007053W obtained on 15th July 2020). The patient consent was waived by the IRB.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**


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