CASE REPORT

Doege-Potter Syndrome: A Rare Paraneoplastic Syndrome of Solid Fibrous Tumors Reported in Indonesia

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ABSTRACT

Introduction: Solitary fibrous tumors (SFT) is a rare group of tumor. Even rarer, it is associated with Doege-Potter syndrome (DPS), which manifests as hypoglycemia due to paraneoplastic syndrome. From searching through national reports and articles, this was the first case of DPS in Indonesia.
Case: A 60-year-old woman was admitted to the emergency department with dyspnea and unconscious. The patient's glucose level showed 21mg/dL. A solid mass on the patient's right lung was shown on the chest X-ray. A previous biopsy concluded that the patient had a solid fibrous tumor with a history of profound hypoglycemia. The patient underwent tumor resection and got a biopsy of the tumor. After resection, the patient showed no sign of hypoglycemia, and the blood glucose level was stable. We concluded that the patient had DPS, a paraneoplastic syndrome associated with the solid fibrous tumor.
Conclusion: Performing an adequate examination and giving prompt treatments can increase the patient's quality of life, even though it is a rare disease and hard to diagnose. The patient's condition, evaluated from a clinical condition, chest X-ray, and blood glucose, was better than before getting radical resection.

INTRODUCTION

Solitary fibrous tumors (SFT), which originate from mesenchymal cells, are rare groups of tumors and often manifest as benign, asymptomatic, and intrathoracic.[1,2] Paraneoplastic syndrome, like Doege-Potter syndrome (DPS), is occasionally associated with these tumors.[3] Karl Doege and Roy Potter first found and described the presence of this syndrome as a non-beta-pancreatic cell tumor. Specifically, a fibrous tumor in the mediastinum that manifests as hypoglycemia in 1930.[4] DPS is a rare paraneoplastic syndrome with an incidence of less than 5% and manifests as hypoglycemia.[5]

DPS presents hyperinsulinemic hypoglycemia from the ectopic secretion of insulin-like growth factor II (IGF-II) from the non-islet cell from a solitary fibrous tumor.[2] SFT is a large, slow-growing tumor that origins from mesenchymal and causes DPS in about 2–4% of cases. Tumoral overproduction of incompletely processed IGF-II is the most common cause of hypoglycemia in this type of tumor.[6]

SFT can be detected early with chest X-ray and appears in imaging examination as a typically homogeneous mass, clearly defined and non-invasive. Computed tomography (CT) scans and magnetic

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resonance imaging (MRI) are considered as effective investigation to determine the invasion of surrounding structures and also suspicion of distant metastases.[7] A biopsy can be performed to confirm the diagnosis. Radical resection is gold standard therapy for SFT and symptoms from DPS, whether for benign or malignant tumors, with or without adjuvant therapy.[8] In this case, the patient also got radical resection, and the blood glucose was stable after the operation, along with an improvement in the clinical condition.

CASE

A 60-year-old woman was admitted to the emergency room due to dyspnea, chest pain, and loss of consciousness a day before. There was no history of diabetes mellitus or alcohol and drug consumption and no sign of vomiting and fever. During admission, the consciousness level was E2M5V2, and the vital signs revealed: blood pressure 150/100 mmHg, temperature 37°C, pulse rate 105 bpm, respiration rate 26, and oxygen saturation 82%. The physical diagnostic found an asymmetrical thoracic expansion with dullness and decreased vesicular breathing sound on the right side. There was no neurological deficit or other abnormality on physical examination. Laboratory results were within normal limits, except the serum glucose was 21 mg/dL (Figure 1). After administering intravenous dextrose solution, the patient gained consciousness with serum glucose at 129. The symptom of hypoglycemia has existed for four months.

On admission, a solid mass on the right lung was revealed on chest X-ray (Figure 2). Chest CT and ultrasonography (USG) revealed a solid mass that obliterated the right lung with minimal effusion (Figures 3 and 4). The biopsy result was a hyperplastic spindle and oval cells with fibrous cells, and the conclusion was a high suspicion of SFT. The patient underwent posterolateral thoracotomy and found a solid tumor, approximately 850 grams, with a size around 19 x 16 x 10 cm (Figure 5). The tumor adhered to the right medial and lower lung. The pathological finding showed fibrous with spindle cells within, staghorn vessels and dominant round chromatin cells, mitosis activity no more than 4/10 high power fields (HPF) with the conclusion of SFT (Figure 6).

On a postoperative day 2, blood glucose level was under control, and the patient was observed in the intensive care unit (ICU). The patient's conditions were getting better, observed from a clinical condition, X-ray, and laboratory. A postoperative chest X-ray showed collapsed lung after surgery due to tumor adherence (Figure 7a). However, on postoperative day 3, chest X-ray showed more expanded lung (Figure 7b). On postoperative day 8, the chest tube was removed and chest X-ray showed less infiltrate and more expanded lung (Figure 7c), followed by better clinical condition and controlled blood glucose. On postoperative day 10, the patient was discharged from the hospital.

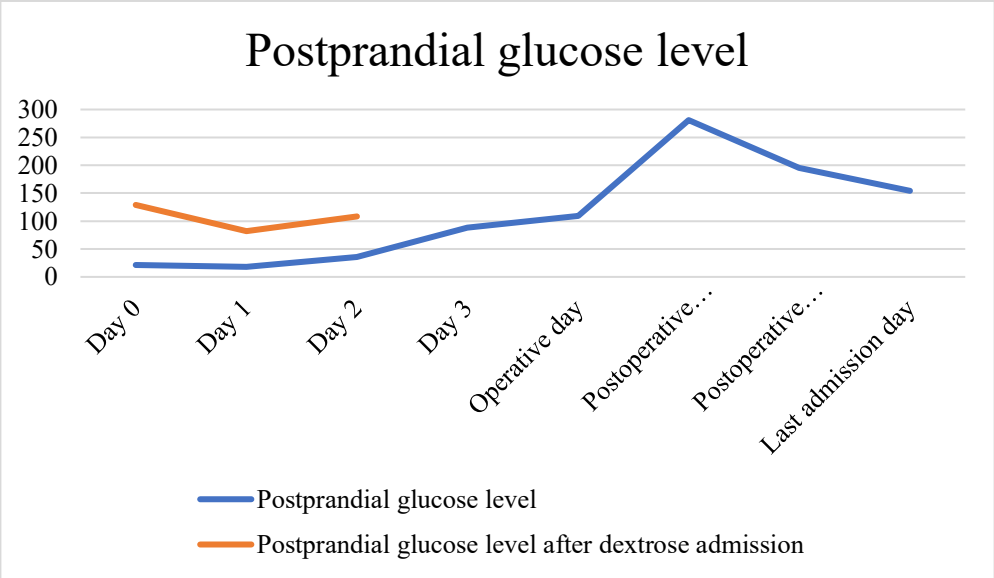


Figure 1. This figure shows the patient's postprandial glucose level on hospital admissions. The charts showed low glucose levels before the operative day and only increased after dextrose admission.

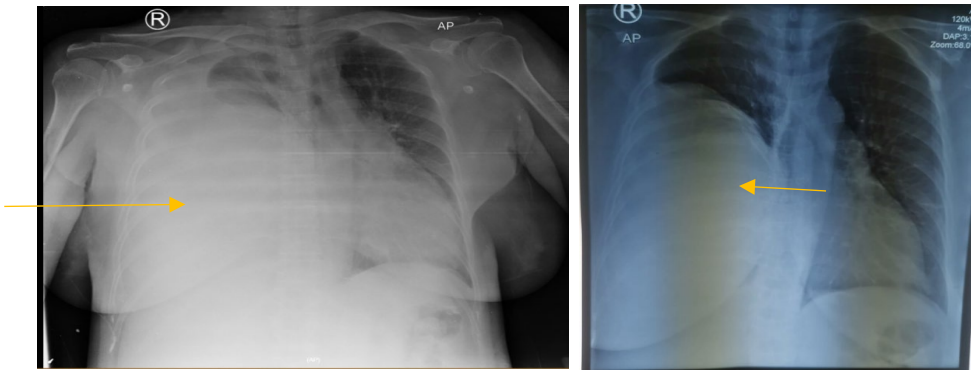


Figure 2. Chest X-ray (a) on admission; (b) four months before admission. Both of the results showed a right mass on the right lung (yellow arrow).

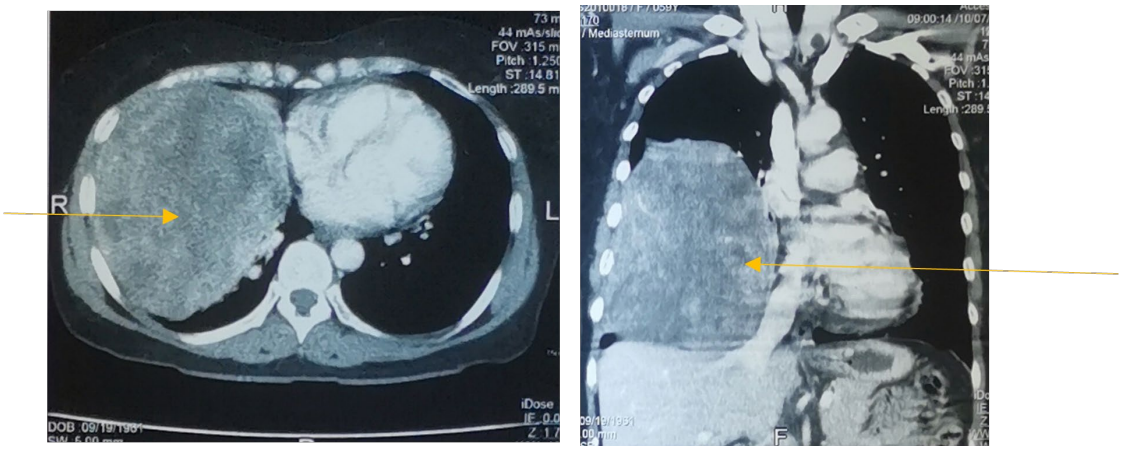


Figure 3. CT scan of thorax revealed solid tumor on the mediastinum (yellow arrow)

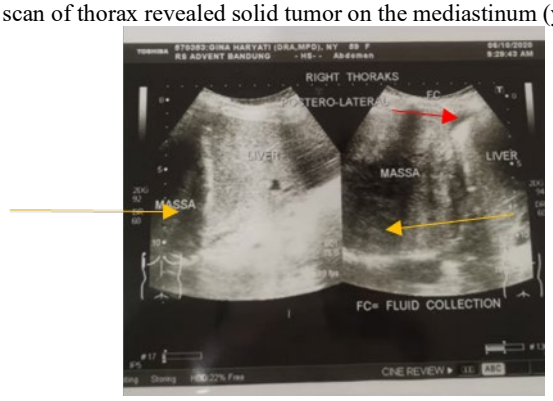


Figure 4. USG thorax from the right posterolateral window showed a mass on the right lung (yellow arrow) and minimal fluid collection (red arrow)

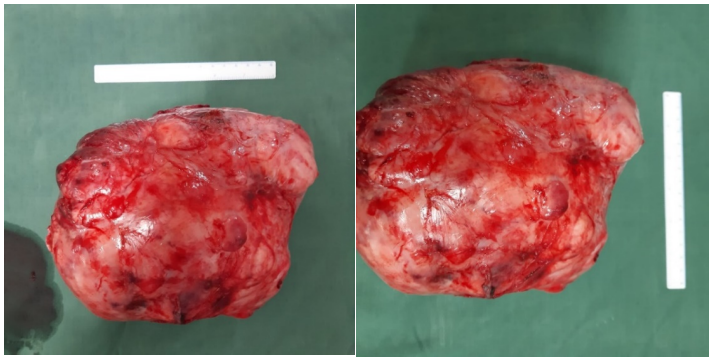
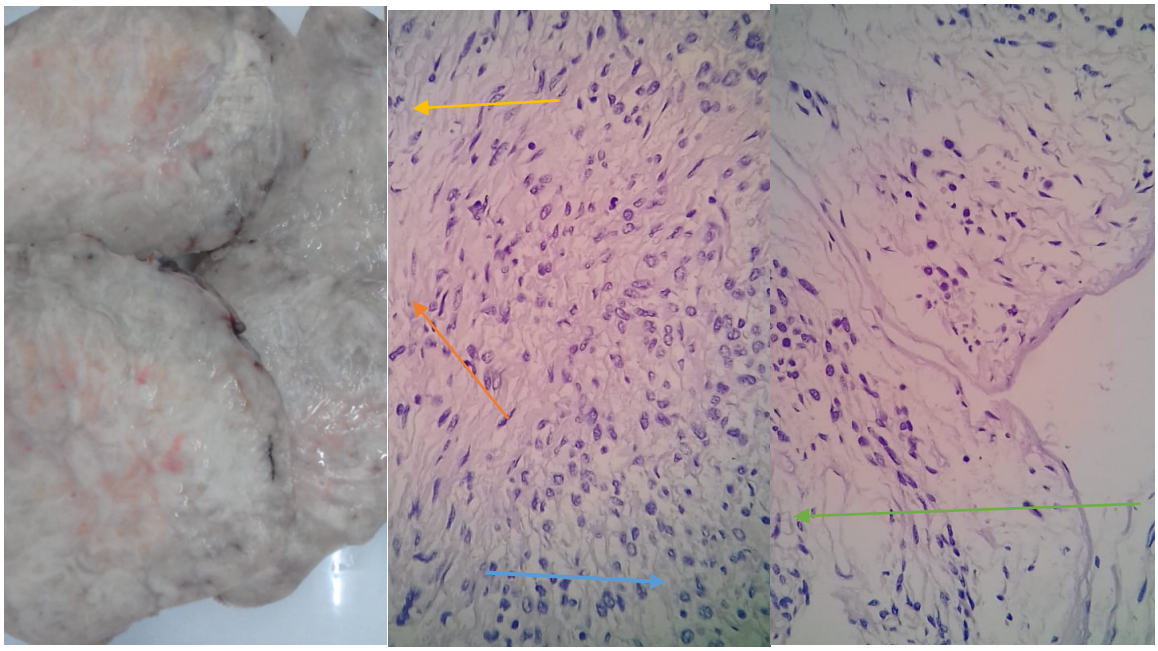
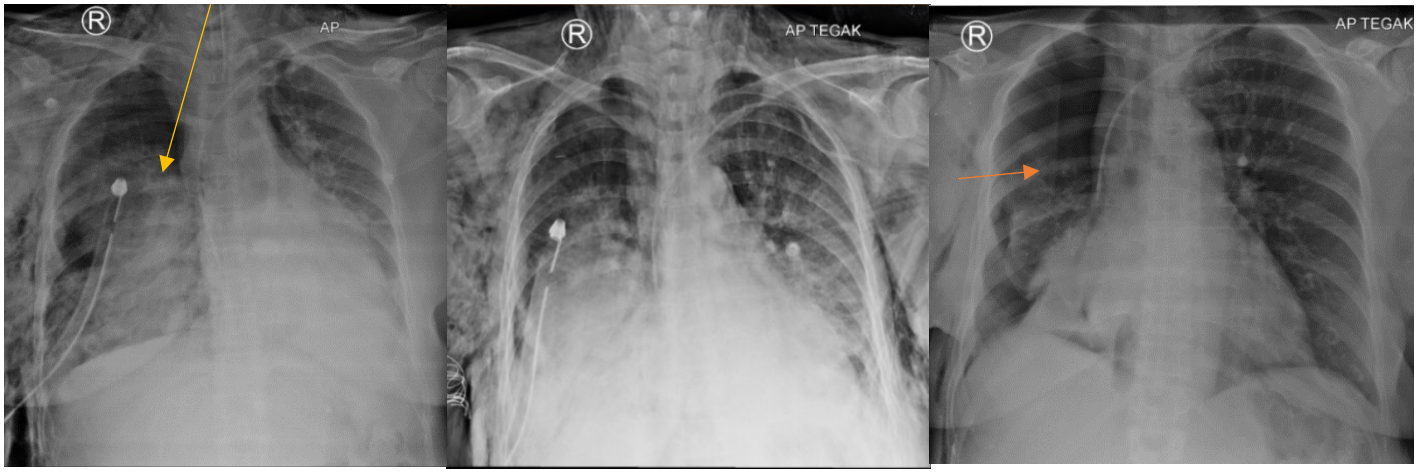


Figure 5. Gross image of solid fibrous tumor after surgery. Approximately 850 grams with a size around 19 x 16 x 10 cm.



(a) (b) (c)

Figure 6. Histopathological findings (a) macro view; (b)(c) micro view showed fibrous (yellow arrow) with spindle cells (orange arrow) within, staghorn vessels (green arrow) and dominant round chromatin cells (blue arrow), mitosis activity no more than 4/10 HPF



(a) (b) (c)

Figure 7. Postoperative chest X-ray (a) postoperative day 1 showed collapsed lung after surgery due to adherence of the tumor (yellow arrow); (b) postoperative day 3 showed more expanded lung; c) postoperative day 8 showed better chest X-ray: less infiltrate, expanded lung. The chest tube was extubated (orange arrow).

DISCUSSION

Fewer than 2,000 cases reported worldwide, SFT is a rare case, with its origins mostly from visceral pleura.[2,9] Recognized first in 1870, the incidence of the case is usually 60-70 years old with a rate of 2.8 of 10,000 people, and it is composed of about 5% of total pleural tumor developments. SFT is usually a benign tumor with an asymptomatic respiratory manifestation like dyspnea or chest pain, it rarely comes with paraneoplastic syndrome.[2,3,9] It is reported that the most common origin of SFT originates from the pleural cavity, followed by the pelvis, liver, retroperitoneum, and kidney. It arises from a wide variety of anatomic sites, extrapleural and intrapleural. In this case, the tumor was extrapleural in the mediastinum.[5,10]

Hypoglycemia, defined by a plasma glucose level <3.0 mmol/L(54 mg/dL), occurs from failure to maintain normal plasma glucose levels. It is an emergency condition that needs quick recognition and prompt treatment to prevent organ damage and mortality.[11,12] When hypoglycemia occurs in SFT patients, it is called DPS, non-islet cell tumor hypoglycemia (NICTH), or a paraneoplastic syndrome that occurs particularly due to IGF-II, which is secreted from fibrous tumor cells.[9] NICTH is relatively rare, and causes spontaneous

hypoglycemia. Having tumor resection is the main therapy for NICTH.[13] Only 45 cases of DPS have been reported from 1979 to 2011, and the incidence is less than 5% as the manifestation of SFT.[5,9]

The pathophysiology and mechanism of hypoglycemia in SFT due to paraneoplastic syndrome caused by a release of an incomplete form of IGF-II excreted ectopically by SFT has a high molecular weight, activates insulin receptors, and terminates hepatic gluconeogenesis. IGF-II has a 50% amino acid sequence similarity to insulin, causing the decreased synthesis of IGF-binding protein because this prohormone suppresses growth hormone. IGF-II that does not bind to IGF receptors in the peripheral tissues or liver will cause a decrease in the release of glucose into the circulation and increase peripheral glucose metabolism. It increases peripheral glucose uptake, binds to IGF-1 receptors, and suppresses insulin release and IGF-1, leading to hypoglycemia. Cytokines such as vascular endothelial growth factor (VGEF) and platelet derived growth factors (PDGF) also play roles in this paraneoplastic condition.[3,5,10] To conclude, tumoral overproduction of incompletely processed IGF-II is the most common cause of hypoglycemia in this type of tumor.[6]

Most patients are diagnosed between 50 and 70 years old due to a typically slow evolution of SFT, hence the development of DPS mostly occurs in elderly age.[14] Hypoglycemia, the main symptom of DPS, can be an early indicator leading to the diagnosis of SFT. In some cases, hypoglycemia may occur after tumor discovery, recurrence, or metastases have occurred.[5,10] Some studies say that DPS in patients without a history of diabetes is relatively uncommon. More differential diagnoses should be considered when the patient responds poorly to dextrose boluses.[15] Respiratory symptoms, however, happen in larger tumors, especially when the diameters are more than 10 or 15 cm, occupying a bigger space, and compressing other thoracic structures. The compression causes respiratory symptoms such as dyspnea, chest pain, cough, and fatigue. The tumor size in this case report happened to be around 19 x 16 x 10 cm, and it was occupying the mediastinum, therefore the patient felt respiratory symptoms like dyspnea and chest pain.[16] Hypokalemia, hyperkalemia, arthropathy, and hypoglycemia have been reported as syndromes associated with benign and malignant SFTs.[17]

SFT, a rare spindle cell tumor, originates from mesenchymal cells, and macroscopically, tumors are usually large lobular masses that are well-circumscribed with a smooth surface and often with a pedicle. Sometimes necrosis, hemorrhage, and calcification can be seen, as seen in this case report.[8] It is described in other studies as a well-circumscribed mass with tan-white homogeneous cut surfaces that can be cystic or hemorrhagic, with sizes ranging from 1 to 20 cm from the pathological perspective.[9] Histologically, SFT is described as patternless growth, storiform arrangement of neoplastic spindle cells in stroma or ovoid with mildly pleomorphic and elongated cytoplasm with hyperchromatic nucleus with variable amounts of collagen and thin-walled branching vessels called staghorn and varying in size and number. Mitotic activity is usually low with <3/10 HPF. In contrast, characteristic of infiltrative margins and hypercellularity with a mitotic index of >4/10 HPF can be obtained in malignant SFTs.[1,18,19]

In this case, the gross revealed 850 grams tumor with dimensions of 19 x 16 x 10 cm with solid white surfaces with yellow necrosis. Histologically, it showed fibrous with spindle cells within, staghorn vessels, and dominant round chromatin cells, and mitosis activity no more than 4/10 HPF which indicated solid fibrous tumor. Levels of serum IGF-I and IGF-II and the ratio of IGF-II to IGF-I are tests to diagnose DPS. However, this test is not widely available and is currently unavailable in our facility.[5,7] Histologic analysis of material obtained by needle biopsy can be used as pre-operative diagnosis of fibrous tumor, especially in pleura.[16]

Imaging examination of fibrous tumor describes as a typically homogeneous mass, clearly defined, and non-invasive. CT scans and MRI are effective investigation to determine the invasion of surrounding structures, including suspicion of distant metastases. The picture on a CT scan is usually a smooth, well-defined, and homogeneous mass. At the same time, MRI demonstrated multi-nodular tumors of iso-intensity or low intensity on T1-weighted images and high signal intensity on T2-weighted images.[10] CT scan can also be used for a follow-up examination to determine any recurrent or metastatic disease. It is recommended to do a follow-up CT scan at six weeks postoperative, especially in suggestive of malignant tumors.[7]

Gold standard therapy for SFT and symptoms of DPS is radical resection, whether for benign or malignant tumors, with or without adjuvant therapy.[8] The resection is recommended both for malignant or benign tumors. The type, location, and technique of surgery depend on the tumor's location, size, and invasion of surrounding structures. Previous studies show complete resolution of hypoglycemia and other symptoms after the resection and surgery, which in this case improved the patient's quality of life. Normalization of glucose level occurs and sometimes postoperatively. Patients can experience episodes of postprandial hyperglycemia due to residual suppressed insulin secretion from pancreatic β cells during the recovery phase, as in this case report.[3,7]

Smaller SFTs are relatively easy to remove, but it is harder to do surgical procedures in giant SFTs, especially when the tumors press mediastinal structures and lungs. Some studies reported that surgery should be

performed via one or two thoracotomies at different levels or via sternotomy,[14] our approach was via right lateral thoracotomy to obtain an optimal view. Chemotherapy and radiation therapy have not been well-studied in patients with SFTs, but it is an alternative therapy when the patient is unsuitable for surgery.[3] Other studies even reported that SFTs are relatively chemotherapy-resistant, with no standard regimens that can be used to treat SFTs and resection of the tumor remains the first choice. Chemotherapy can be considered if surgery cannot be performed or tolerated.[5]

SFT can recur within months and years of resection, with recurrence rates around 2-4% for benign and 14- 68% for malignant tumors. It is reported that recurrence is more common with extrathoracic tumors.[3,7] Nonetheless, malignant behavior has been reported in up to 12%.[20] In several studies, most SFTs are benign, but as for malignant, 10-15% will metastasize. The recurrence can be a prognostic factor for a patient's quality of life. It should be under observation within 24 months of resection.[3]

Huge size over 15 cm and elder age more than 55 years old were predicted to have a poor outcome and prognosis.[5,9] This was a benign tumor based on histological features, but the patient's condition should be evaluated especially in the next 24 months. Due to the patient's age, tumor size, and lung function, CT scan and clinical condition should be evaluated intensely. DPS is potentially life-threatening with both diagnosis and management require extra attention and must be appropriately handled despite its difficulty.[17] From searching through national articles and reports, this was the first case of DPS in Indonesia.

CONCLUSION

SFT is a rare group of tumors, and even rarer, it presents as a paraneoplastic syndrome named DPS that manifests as hypoglycemia. It is reported in fewer than 2,000 cases worldwide, hence it should be recognized properly, an adequate examination should be performed, and prompt treatments should be given to increase the patient's quality of life. In this case report, the patient's condition was evaluated from a clinical condition. Chest X-ray and blood glucose were better than before getting radical resection. Due to the quick recognition and radical resection as the main therapy for DPS, the patient's outcome was good, even though it was still being evaluated intensely.

Consent

Written informed consent was obtained from the patient.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Conceptualizing and initiating case report: JTW, EN, and PS. Collecting and analyzing data (interpretation): JTW, PS, EN, AP, YH. Drafting and making manuscript: EN and AP. Critical revision of the manuscript: EN. All authors reviewed and approved the final version of the manuscript.

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