

## CASE REPORT

# Large pleural tumor revealed by severe hypoglycemia: Doege–Potter syndrome

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## Abstract

**Aim:** Doege–Potter syndrome is a rare condition consisting of a mesenchymal tumor, either benign or malignant, accompanied by severe hypoglycemia. The syndrome was first described independently by two American physicians, Karl Walter Doege (1867–1932) and Roy Pilling Potter (1879–1968), in 1930, but it was not before 1988 that it was associated with non-islet cell tumor production of insulin growth factor (IGF) that induces hypoglycemia as a paraneoplastic syndrome. **Case presentation:** We present the case of a 61-year-old woman with severe hypoglycemia that induced seizures. On the general check-up, a massive tumor occupying the lower part of left hemi-thorax was discovered. Initially, corticosteroids, glucose i.v. and high carbohydrate diet managed to prevent the severe blood glucose drop. Surgery exposed a massive well-defined pleural tumor. After surgical removal, blood glucose stabilized. Histological examination confirmed the fibrous tumor that proved to be malignant on immunochemistry. **Discussion:** The authors discuss other cases reported in the literature of this rare condition and its pathogenic mechanisms, the presented case being the first reported in Romania. **Conclusions:** The clinician should be aware of the possible existence of a pleural tumor in a patient presenting an unexplained hypoglycemia because the surgical removal of the tumor can solve the clinical manifestations.

**Keywords:** Doege–Potter syndrome, fibrotic solitary pleural tumor, hypoglycemia, malignancy.

## Introduction

Doege–Potter syndrome is a rare paraneoplastic syndrome, consisting of the association of symptomatic hypoglycemia with a solitary fibrous tumor of the pleura (SFTP). The syndrome was first described in 1930 independently by Karl Walter Doege (1867–1932) and Roy Pilling Potter (1879–1968), who reported each one case of a massive pleural tumor discovered in patients with symptoms related to severe hypoglycemia [1, 2]. It was not until the eighties when the cause of hypoglycemia was identified, by demonstrating the production of insulin-growth factor (IGF) within the tumor cells, with paraneoplastic hypoglycemia manifestations.

## Case presentation

We present the case of a female patient, age 61, from a rural area, presenting in the Emergency Department for restlessness and seizures in the previous day. She was admitted initially in the Neurology Department with suspected epilepsy, where a blood glucose of 30 mg/dL was measured. The patient was referred to a Diabetes and Nutrition Clinic, where the same low glucose levels were present, ranging from 30 to 50 mg/dL. A pancreatic insulinoma was suspected as the source of an inappropriate insulin secretion with consecutive hypoglycemia. The patient underwent a thoracic and abdomen computed tomography (CT) scan that ruled out a pancreatic tumor, showing instead the presence of a massive tumor in the left hemi-thorax. The patient was consequently referred to the Pulmonology Department for further investigations.

The medical history of the patient, a nonsmoker, mother of four, revealed a left side spastic hemiparesis known since childhood and never investigated, associating significant muscle atrophy in the upper and lower left limbs and impaired function of the limbs.

Physical examination showed a low body mass index (BMI), no fever, oxygen saturation of 98% in ambient air, with complete absence of lung murmur and dullness on the left hemi-thorax.

The CT scan showed in the left hemi-thorax a massive tumor of about 20 cm, with inhomogeneous structure, in contact with the lateral thoracic wall, well defined against the lung parenchyma, which it partially compressed, with no lymph node enlargement in the mediastinum (Figure 1).

Blood chemistry revealed glucose levels between 50 and 70 mg/dL.

The other chemistry tests were normal, with no inflammatory syndrome.

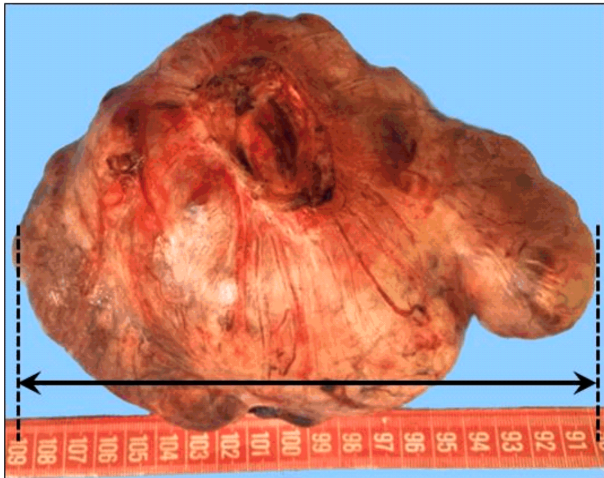
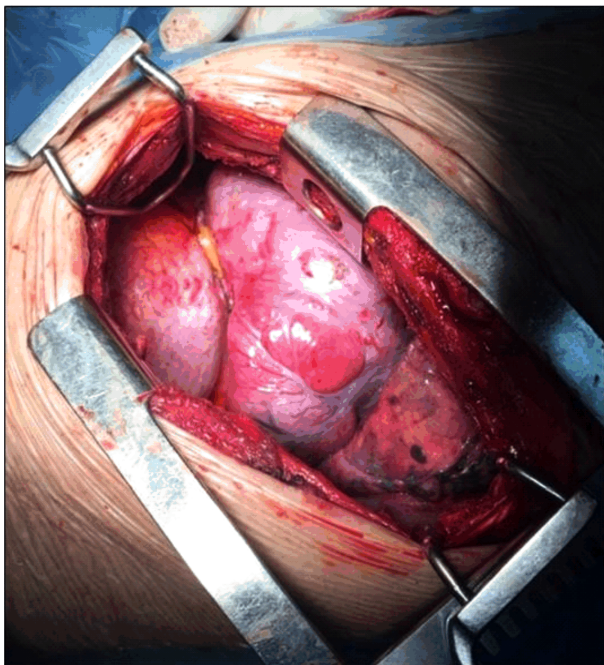
Spirometry showed a restriction with a vital capacity of 1.68 L (62% of predicted value).

Immediately after admittance, the patient received a diet rich in carbohydrates with slow glucose release and systemic corticosteroids (i.v. Hydrocortisone, 200 mg/day). Intravenous Glucose solutions were administered in case the blood glucose dropped under 50 mg/dL.

Surgery was performed with a posterior–lateral thoracotomy in sixth left intercostal space. A large tumor was revealed, located in the posterior and inferior region of the pleural cavity, tightly adhering to the diaphragm and pushing the lung forward and upward (Figure 2).



**Figure 1** – CT scan with i.v. contrast showing a massive tumor at the base of the left hemithorax, with parietal contact, well defined against the lung.



**Figure 2** – (A) Aspect during surgery, showing the massive pleural tumor occupying almost the entire operative field, and (B) the resected tumor.

The lung adhesences were easily removed, but the tight contact to the diaphragm imposed the partial resection of a diaphragm roundel for complete release of the tumor. We noted that the tumor had two main vascular pedicels, both originating in the visceral pleura of the left lung.

The excised tumor had an oval shape, capsulated, measuring 18.5 cm on the longer axis (Figure 2).

The postoperative evolution was marked by the difficult re-expansion of the left lung and a chylothorax occurring in 3<sup>rd</sup> day after surgery associated to the thrombosis of the internal jugular vein, possibly related to the catheterization of the vein. The treatment of the chylothorax was conservative, including complete restriction of food and fluid oral intake, parenteral infusion of food and fluids, removing of the jugular catheter and anticoagulant treatment. Initially, the daily drainage of the chylous pleural fluid was up to 1000 mL, but in the subsequent days, the pleural fluid clarified and the drainage volume diminished (Figure 3).



**Figure 3** – Chest X-ray seven days after surgery, showing poorly expanded left lung and efficient drainage of the chylothorax.

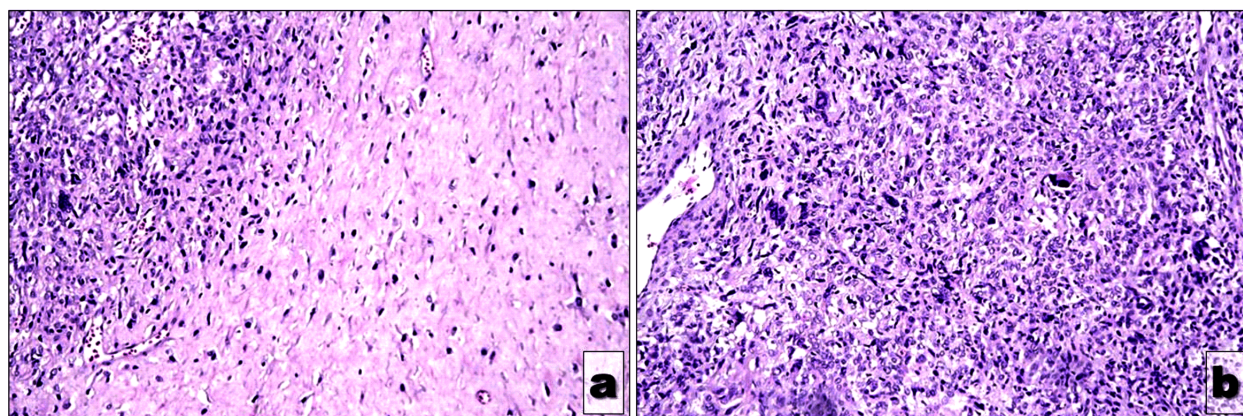
After seven days, the patient was allowed to drink water, then eat non-fat food. The pleural drainage could be removed in the 14<sup>th</sup> day after surgery, with no recurrence of the chylothorax, and complete expansion of the left lung.

The blood glucose levels after surgery ranged between 100 and 109 mg/dL, with no other medical intervention. The patient was discharged in good condition.

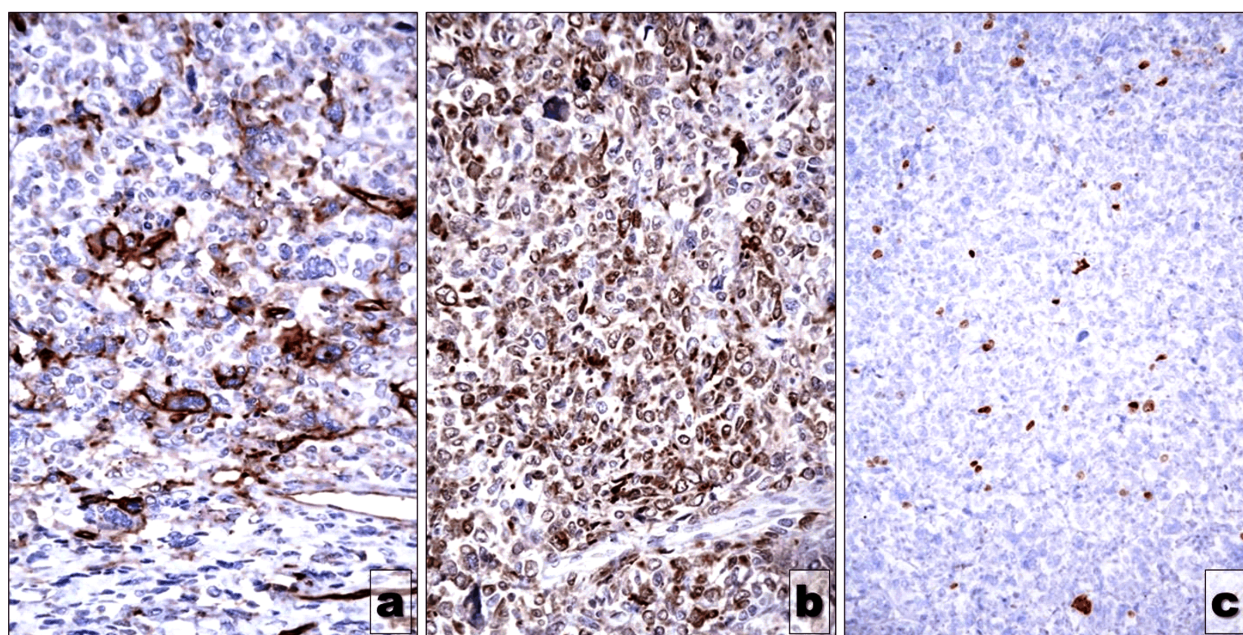
The pathological examination of the tumor showed a heterogeneous tumor proliferation of spindle cells and giant multinucleated cells (Figure 4). Frequent atypical nuclear shapes were noted, but with minimal atypical mitoses (less than 4 mitoses/2 high power fields – HPFs).

Immunohistochemistry of the tumor tissue showed a higher frequency of atypical mitoses, positive staining for CD34 on the tumor cell membrane, diffuse cytoplasmic staining for Bcl-2, negative staining for CD99, and Ki67 – approximately 6% mitotic index in the tumor cells (Figure 5).

The final diagnosis was of low-grade malignant fibrous solitary pleural tumor.



**Figure 4** – Histological aspect of the pleural tumor, showing spindle cells (a) and scattered giant multinucleated cells (b). HE staining,  $\times 40$ .



**Figure 5** – Immunohistochemistry of the tumor: (a) Positive staining for CD34,  $\times 200$ ; (b) Positive staining for Bcl-2,  $\times 100$ ; (c) Ki67-mitotic index,  $\times 40$ .

## Discussion

Solitary fibrous tumors of the pleura originate in the mesenchymal tissue of the pleura, unlike mesotheliomas, originating in the pleural mesothelium [3, 4].

SFTPs can be benign (in a proportion of about 80%) or malignant (fibrosarcomas) and can be unique or have multiple locations. Similar tumors can develop in other mesenchymal tissues and can be seen in abdominal cavity or in the retroperitoneum [3, 5].

SFTPs can be accompanied by a multitude of paraneoplastic syndromes that can be the initial clinical manifestation of the tumor. Association of SFTP with several syndromes was described in the literature: acromegaly, seborrheic keratitis [6], Pierre Marie hypertrophic pneumic arthropathy (described in 10 to 20% of benign or malignant cases) [7], hyper- or hypokalemia [8], etc. The paraneoplastic syndromes are generated by the paracrine secretion within the tumor of several molecules with endocrine action, or epithelial growth factors.

Less than 5% of SFTPs are associated with hypoglycemia, taking the form of Doege–Potter syndrome, a

very rare entity [9]. These tumors have a typical pathological structure, with spindle cell arrangement, staining positive for CD34 and vimentin [10]. They have been reported also in the abdomen and the head and neck regions.

Doege–Potter syndrome was first described in 1930, separately by a surgeon, K.W. Doege, and a radiologist, R.P. Potter, who presented two cases of massive pleural tumors accompanied by clinical manifestations attributable to hypoglycemia [1, 2]. Anyway, it was not before 1988 that the association between the pleural fibrous tumor and the increased production of IGF, responsible for the hypoglycemia, was demonstrated.

SFTPs associating hypoglycemia are very rare. A paper published in 2014 analyses 45 cases reported in the literature since 1979 [11]. In this article, almost half of the tumors were malignant, with an even gender distribution.

Typically, spontaneous hypoglycemia can be caused by an increased insulin level, similar to the insulin substitutive treatment for diabetes mellitus. In patients with a syndrome generated by an inappropriate endogenous insulin secretion, the first hypothesis is a pancreatic

insulinoma. Other non-islet cell tumors can induce the same effect, like liver, kidney, lung, pleura, breast, head and neck tumors, hemangiopericytoma, leukemia or lymphomas [12].

Anyway, a low level of serum insulin and the absence of ketoacidosis suggest that hypoglycemia is not generated by an excess of endogenous or exogenous insulin.

An effect similar to a high insulin level can be determined by the secretion of IGFs within some tumors, resulting in non-islet cell tumor hypoglycemia. Following mutations in the tumor cells, they have an aberrant secretion of the pro-hormone big-IGF2 [10]. The effects of big-IGF2 are fulfilled by its affinity for IGF1 and IGF2 receptors, with the consequence of cell growth stimulation, suppression of pituitary secretion of growth hormone followed by the suppression of endogenous secretion of IGF1 and insulin. The activation of IGF1 receptors by big-IGF2 can induce clinical consequences like acromegaly or seborrheic keratosis. The goiter described in one case reported can equally be generated by the stimulating influence of big-IGF2 on the thyroid gland [13].

Typically, 80% of mature circulating IGF2 is inactive, bound to the insulin growth factor binding protein 3 (IGFBP3) and to another ligand. In patients with non-islet cell tumor, big-IGF2 accumulates, most of it being bound only to IGFBP3. The result is a smaller molecule, with a lower molecular weight, able to cross the endothelial barrier, spread into the blood and act on insulin receptors [14–17].

It was suspected that hypoglycemia results from an increased consumption of glucose within the tumor, but it was demonstrated that hypoglycemia in this case is due to an increased glucose uptake, lower insulin and glucagon secretion, decreased lipolysis and liver gluconeogenesis, which are effects of the massive secretion of big-IGF2 [18, 19].

Most tumors accompanied by hypoglycemia reported were massive tumors, suggesting that the hypoglycemic effect increases in parallel with the increase of the tumor mass [20, 21].

The diagnosis of Doege–Potter syndrome can be sustained by a low blood level of growth hormone and IGF1, and a decreased IGF2:IGF1 ratio. A high level of IGF2 is a strong argument in favor of the diagnosis. All these arguments are difficult to obtain, as only few laboratories have the capability to perform these tests.

The diagnosis of the syndrome is ultimately confirmed by the resolution of hypoglycemia after the surgical removal of the tumor [12], as it happened also in our patient.

The treatment of Doege–Potter syndrome is based on the surgical removal of the tumor, which usually leads to immediate resolution of the hypoglycemia. While waiting for the operation, the patient can be treated with corticosteroids that improve immediately the hypoglycemia. Moderate and high doses can even reduce the tumor mass [22]. The patient may benefit from a high carbohydrate diet, including slow glucose releasing foods, and infused Dextrose if the blood glucose level drops under 50 mg/dL [5].

Long-term prognosis is generally good, but recurrence of the tumor may appear in the years following surgical resection. The recurrence rate is similar for benign and malignant tumors [11].

In our patient, the diagnosis work-up was triggered by the initial neurological symptoms generated by the hypoglycemia, initially considered as epileptic seizures. The patient was already suffering of a left hemiparesis, associated with important hypotrophy of muscles on the left side that was never investigated before, favoring the suspicion of a primary neurological condition at presentation. Anyway, her older condition seemed unconnected to the recent symptoms.

Hypoglycemia resolved immediately after surgery. The tumor had a macroscopic and histological appearance of a benign pleural fibrous tumor, but the immunohistochemical analysis showed a low-grade malignancy.

To our knowledge, no other clinical cases of Doege–Potter syndrome were previously reported in Romania.

## Conclusions

Although Doege–Potter syndrome is a very rare entity, the presence of an unexplained hypoglycemia in a patient should determine the clinician to investigate the presence of a pleural tumor whose cells could have an increased paracrine secretion of IGF2 because the surgical removal of the tumor will result in the disappearance of the paraneoplastic symptoms although the long-term prognosis is marked by the risk of recurrence, and of malignant evolution, with possible remote metastasis.

## Conflict of interests

The authors declare that they have no conflict of interests.

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