DOEGE-POTTER SYNDROME: A CASE REPORT AND AN UPDATE REVIEW

Roser Fort-Culillas[1*], Rebeca Barahona San Millán[2*], Isabel Garcia-Fructuoso[1], Angels Quera González[3], Armand Grau Martín[4,8], Montserrat Puigdemont Guinart[5], Jordi Rubió-Casadevall[1,6,8] , Mònica Recasens Sala[2,8], Rut Porta Balanyà[1,7,8]

1. Medical Oncology Department, Institut Català d'Oncologia (ICO), Girona, Spain.
2. Department of Endocrinology, Hospital Universitari Dr JosepTrueta de Girona, Girona, Spain.
3. Department of Pathology, Hospital de Figueres, Figueres, Spain.
4. Department of Internal Medicine, Hospital de Figueres, Figueres, Spain.
5. Girona Cancer Registry , Girona, Spain
6. Genetic Descriptive, Genetic and Prevention Epidemiology Group. Biomedical Research Institute of Girona (IDIBGI), Spain.
7. New Therapeutics Cancer Research Group, TargetLab. Girona University. Girona, Spain.
8. Medical Sciences Department, School of Medicine, Girona University, Girona, Spain.

Corresponding author:

Rebeca Barahona San Millán

rbarahona.girona.ics@gencat.cat

KEY WORDS:

Doege-Potter syndrome; solitary fibrous tumour; paraneoplastic syndrome; hypoglycemia; STAT6; big-IGF2.

KEY CLINICAL MESSAGE:

Paraneoplastic Doege-Potter syndrome in a patient with solitary fibrous tumor successfully treated with medical management.

INTRODUCTION

In 1930, Karl Doege and Roy Potter, described an infrequently paraneoplastic syndrome characterized by non-islet cell tumor hypoglycemia (NICTH) mostly associated with solitary fibrous tumors (SFT), nowadays known as Doege-Potter syndrome (DPS).[1]

SFT is an uncommon tumor with a mesenchymal origin, it has 12-13% rate of malignancy, mostly located in the pleura.[2]

DPS is defined as NICTH associated with a SFT and has only been reported in <5% of SFT cases.[1]

We present a case of diagnosis and management of DPS in a patient with an extrapleural malignant SFT.

CASE PRESENTATION

A 31-year-old Latin American woman with no previous pathological medical history was admitted to the emergency room with episodes of sweating, tremors and decreased level of consciousness with documented hypoglycemia. A right indurated malar mass, measuring up 10 cm was observed.

She explained a three year evolution right malar tumor, its appearance coincided with an exodontia. A surgical resection was proposed in her country, but finally was not performed.

Blood test showed a non-insulin-mediated hypoglycemia (24 mg/dl [70-110mg/dl]) with low levels of insulin (0,26 µIU/mL [2,00 - 25,00 µIU/mL]), C-peptide (0,10 ng/Ml [1,10 - 4,40 ng/mL]) and proinsulin (0,68 pmol/L [0,5 - 3,5 pmol/L]).

Hypoglycemia with hypoinsulinemia secondary to severe hepatic insufficiency and cortisol deficiency was ruled out. The sulfonylureas test was negative. We also measured IGFII (1040 ng/mL[442 - 1049 ng/mL]), IGFI (46,1ng/ mL [109 - 284ng/mL]) and IGFBP3 (3,8mcg/mL[3,0 - 7,8 mcg/mL]).

A CT scan was performed and showed a solid tumor from the right temporal region to the nasopharynx, contacting the parotid gland, affecting the neck structures, with a destruction of zygomatic arch. Hepatic metastases were also shown with no other findings.

The MRI revealed a mass of 95x69x61mm, invading the right intratemporal fossa, the right pterygopalatine fossa and the right parotid space.

Octreotride scan demonstrated significant uptake of label by the tumor indicative of the presence of somatostatin receptors in the malar lesion, in contrast to a low uptake in the hepatic lesions.

The facial biopsy showed a cellular spindle cell neoplasm having uniform fibroblastic cytomorphology, a patternless architecture thin-walled branching vessels with focally prominent hyaline collagenous stroma. The biopsy from the liver showed similar features but was more cellular, with mildly increased nuclear atypia and showed readily identified mitotic figures, numbering up to 12 x10 high-power fields. An extensive immunohistochemistry study was performed over both biopsies, which showed negativity for CD34 and strong and diffuse nuclear positive staining for STAT6 in all tumor cells [figure1]. Cell proliferation marker Ki67 resulted 5 % in the facial biopsy and 20 % in the hepatic biopsy. The case was finally diagnosed as a malignant SFT.

Initially, the patient required a continuous supply of 10% glucose solution associated with corticosteroid therapy and a high intake of carbohydrates to solve and avoid episodes of hypoglycemia.

She commenced treatment with long-acting subcutaneous octreotide. This allowed the removal of the serum and a reduction in the corticosteroid therapy.

Chemotherapy with adriamycin and ifosfamide was initiated and she received a total of 4 cycles. The follow- up with CT scan showed a reduction of the primary tumor (50x70x55 mm) and a hepatic progression in number and size of the lesions.

Eventually, the patient decided to return to her home country, so, further treatment and subsequent follow-up could not be continued.

DISCUSSION

DPS is a rare clinical entity and manifests itself as hypoglycemia associated with a SFT.

Hypoglycemia occurs because of the overproduction of the incomplete form of the insulin growth factor, known as big-IGF2, by the tumor.[1,3] Increased glucose intake has also been reported in tumors of more than 10cm, a measurement similar to the reported case.

Given the impossibility to directly measure big-IGF2, the ratio of IGF2:IGF1, an indirect marker used to quantify the mentioned levels, was performed. The 3:1 ratio is considered normal while the clinically significant level is above 10. Levels measured in our case were up to 22.

The most characteristic (albeit nonspecific) immunohistochemical finding is CD34 expression, however 5% of the STF may be negative. The NAB2-STAT6 gene fusion, resulting in a chimeric protein (STAT6), was identified as a consistent finding in SFT. Nuclear expression of the carboxy terminal part of STAT6 is a highly sensitive and almost perfectly specific immunohistochemical marker for SFT and can be helpful to distinguish this tumor type from histologic mimics.[4]

In our case immunohistochemistry for CD34 was negative. However, all tumor cells showed strong and diffuse nuclear positivity for STAT6, being consistent with the diagnosis of SFT.

Functionality tests showed an increased octreotide uptake in the primary tumor contrasting with fewer uptakes in the liver metastases. It is not uncommon to objectify a different behavior in growth, as well as response to treatment, between the primary tumor and the metastases.

The increased expression of somatostatin receptors in the malar tumor matches with a greater response in contrast to the progression of hepatic metastasis. The discordance in the Ki67 index (lower in the primary tumor) is also remarkable.

The treatment of choice of SFT is surgical resection and usually resolves hypoglycemia definitively.[3] The medical management of hypoglycemia includes oral or intravenous glucose therapy, corticosteroids and somatostatin analogues.

We have analyzed the crude incidence rate of the STF in our geographical area (728.734 inhabitants according to the census, (www.idescat.cat) since 1999 to 2016, using data from the Girona Cancer Registry. Crude incidence rate was 0,262 cases per 100000 inhabitants-year, supporting the data that the SFT is a rare entity.[5]

In our cohort 35 SFT were diagnosed, 15 were malignant (43%), mainly located in the thorax (59%). Twelve were localized and could be removed by surgery. Three received also radiotherapy. The 3 diagnosed in advanced stage of the disease, 2 received exclusively chemotherapy and one best supportive care.

CONCLUSION

DPS is a rare paraneoplastic syndrome associated to SFT, whose physiopathological mechanism is difficult to demonstrate, however medical management can control symptoms regardless of the results of the chemotherapy treatment.

CLINICAL KEY MESSAGE

Paraneoplastic Doege-Potter syndrome in a patient with solitary fibrous tumor successfully treated with medical management

AUTHOR CONTRIBUTION

1. **Roser Fort-Culillas**

   Medical Oncology Department, Institut Català d'Oncologia (ICO), Girona, Spain
   rfort.girona.ics@gencat.cat

   Main autor. Collected the data, performed the analysis and wrote the paper.

2. **Rebeca Barahona San Millán**

   Department of Endocrinology, Hospital Universitari Dr Josep Trueta de Girona, Spain
   rbarahona.girona.ics@gencat.cat

   Coauthor and corresponding autor. Collected the data, performed the analysis and wrote the paper

3. **Isabel Garcia-Fructuoso**

   Medical Oncology Department, Institut Català d'Oncologia (ICO), Girona, Spain
   igarciaf.girona.ics@gencat.cat

   Wrote the paper and analysis the data.

4. **Àngels Quera González**

   Department of Pathology, Hospital de Figueres, Figueres, Spain
   MAQUERA@salutemporda.cat

   Performed the pathological diagnosis.

5. **Armand Grau Martín**

Department of Internal Medicine, Hospital de Figueres, Figueres, Spain
Medical Sciences Department, School of Medicine, Girona University, Girona, Spain
agrau@salutemporda.cat

Diagnosis and initial treatment of the patient. Revising the work for important intellectual content.

6. **Montserrat Puigdemont Guinart**

Institut Català d'Oncologia Girona, Cancer Registry, Spain
mpuigdemont@iconcologia.net

Collected the data and contributed to the analysis of the data.

7. **Jordi Rubió Casadevall**

Medical Oncology Department, Institut Català d'Oncologia (ICO), Girona, Spain
Genetic Descriptive, Genetic and Prevention Epidemiology Group.Biomedical Research Institute of Girona (IDIBGI). Spain
Medical Sciences Department, School of Medicine,Girona University, Girona, Spain
jrubio@iconcologia.net

Revising the work critically for important intellectual content and cancer treatment.

8. **Mònica Recasens Sala**

Department of Endocrinology, Hospital Universitari Dr JosepTrueta de Girona, Spain
Medical Sciences Department, School of Medicine,Girona University, Girona, Spain
mrecasens.girona.ics@gencat.cat

Revising the work critically for important intellectual content and endocrine treatment.

9. Rut Porta-Balanyà

Medical Oncology Department, Institut Català d'Oncologia (ICO), Girona, Spain
New Therapeutics Cancer Research Group, TargetLab. Girona University. Girona, Spain
Medical Sciences Department, School of Medicine,Girona University, Girona, Spain
rporta@iconcologia.net

Revising the work critically for important intellectual content. Final approval of the version to be published.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ACKNOWLEDGEMENTS

We thank Katie Linder for reviewing the English language of the manuscript.

REFERENCES

1. Ogunsakin AA, Hilsenbeck HL, Portnoy DC, Nyenwe EA. Recurrent Severe Hypoinsulinemic Hypoglycemia Responsive to Temozolamide and Bevacizumab in a Patient With Doege-Potter Syndrome. Am J Med Sci. 2018;356(2):181-184.

2. Zafar H, Takimoto CH, Weiss G. Doege-Potter syndrome: hypoglycaemia associated with malignant solitary fibrous tumor. Med Oncol. 2003; 20(4):403-8.

3. Khowaja A, Johnson-Rabbett B, Bantle J, Moheet A. Hypoglycemia mediated by paraneoplastic production of Insulin like growth factor-2 from a malignant

renal solitary fibrous tumor-clinical case and literature review. BMC EndocrDisord. 2014;14:49.

4. Doyle LA, Vivero M, Fletcher CD, Mertens F, Hornic JL. Nuclear expression of STAT6 distinguishes solitary fibrous tumor from histologic mimics. Mod Pathol 2014; 27:390-395.

5. Thorgeirsson T, Isaksson HJ, Hardardottir H, Alfredsson H, Gudbjartsson T. Solitary fibrous tumors of the pleura: an estimation of population incidence. Chest. 2010;137(4):1005-6.

FIGURES

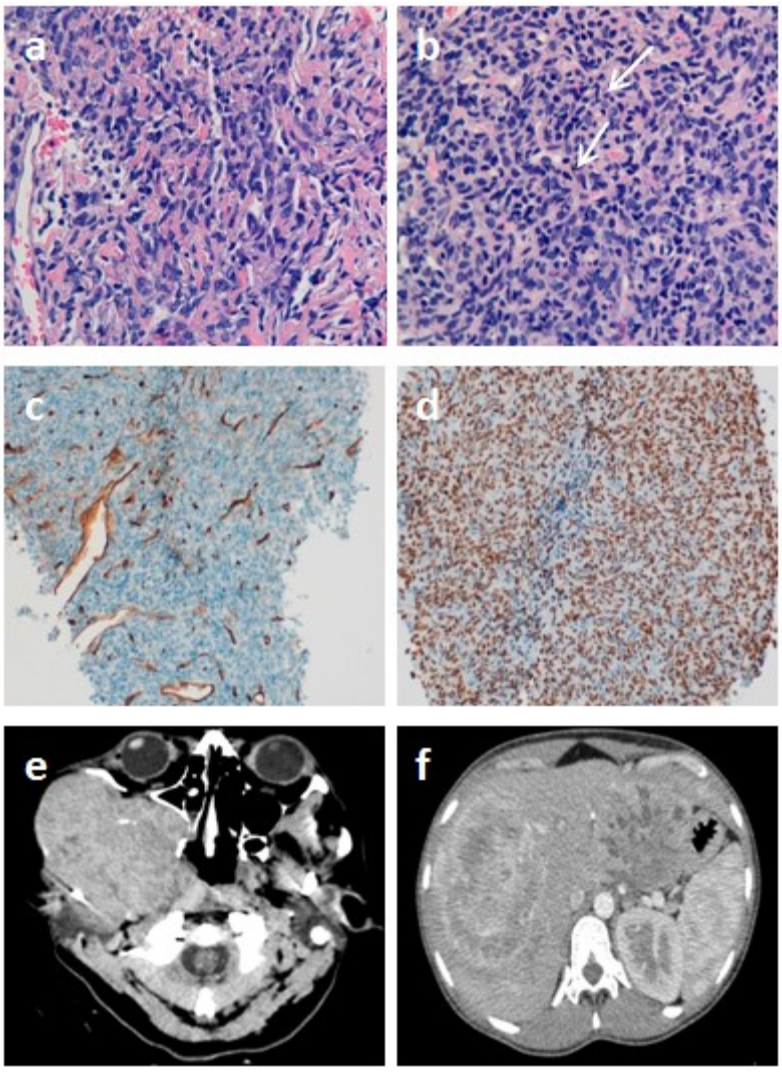

Figure 1. a-d: histology and immunohistochemistry of TFS. **(a)** Facial biopsy: fusiform cell tumor with fibroblastic appearance and uniform extension without architectural pattern and branched vessels with thin walls. **(b)** Liver biopsy: tumor of similar characteristics, but more cellular, with greater nuclear atypia and with evidence of mitotic figures (arrows). **(c)** CD34 marker is negative in tumor cells, with positive internal control at the vascular walls. **(d)** STAT6 shows a uniform, diffuse and intense nuclear expression in tumor cells. **e-f: CT images. (e)** Extensive expansive lesion in the right chewing space. **(f)** Liver with multiple metastatic lesions. The two largest lesions, in segment III of 110 mm and segment VIII of 150 mm.