A Rare Diagnosis After the Fall of a 96-Year-Old Woman: Doege-Potter Syndrome

Angela Ida Pincelli1, Mario Perotti1, Francesca Massariello3, Antonella Gatti1, Damiano Calella1, Vincenzo Cimino1, Justin Haas4, Giuseppe Bellelli2,3,5, Paolo Mazzola3,5,* and Giorgio Annoni2,3,5

1San Gerardo Hospital ASST Monza, Division of Internal Medicine, Monza, Italy; 2Acute Geriatrics Unit, Monza (MB), Italy; 3University of Milano-Bicocca, School of Medicine and Surgery, Monza (MB), Italy; 4University of Alberta, Edmonton, Canada; 5NeuroMI – Milan Center for Neuroscience, Clinical Neurosciences Research Area, Milano (MI), Italy

Abstract: Introduction: Doege-Potter Syndrome (DPS) is a rare but life-threatening paraneoplastic syndrome, characterized by Non-Islet Cell Tumor-Induced Hypoglycemia (NICTH) secondary to a Solitary Fibrous Tumor (SFT), which secretes an incompletely processed form of Insulin-like Growth Factor 2 (IGF-2).

Results: A 96-year-old woman was admitted with head trauma due to an accidental fall. During her hospital stay she experienced frequent hypoglycemic episodes. Multiple injections of 33% dextrose and continuous infusion with 10% dextrose were required to maintain normal blood glucose levels. Biochemical analyses revealed hypoinsulinemic hypoglycemia, low C-peptide levels, suppressed insulin-like growth factor-1, normal insulin-like growth factor-2, and an elevated IGF-2:IGF-1 ratio, all consistent with IGF-2 secretion by a non-islet cell tumor.

A contrast-enhanced chest and abdominal CT scans showed a single large pleural mass in the left lower hemithorax measuring 15x14 cm without secondary lesions. Histological analysis of biopsied specimens suggested a solitary fibrous pleural tumor; accordingly, a diagnosis of Doege-Potter syndrome was considered.

Due to extensive tumor burden and the advanced age of the patient, supportive and non-invasive management was chosen. Dexamethasone therapy was started, and while receiving this therapy she was able to discontinue glucose infusion and successfully maintain euglycemia.

Discussion: In the elderly, a sudden and unexplained fall can be the expression of severe hypoglycemia, usually as a complication of insulin therapy or of oral hypoglycemic agents administered to patients with diabetes. However, in patients without diabetes, other causes should be investigated, and the hypothesis of neoplastic diseases should be considered.

Conclusion: In this case report we describe an uncommon cause of paraneoplastic hypoglycemia occurring in the oldest patient with a non-islet cell tumor reported thus far.

Keywords: Doege-potter syndrome, solitary fibrous tumor, hypoglycemia, IGF, fall, lower hemithorax measuring.

1. INTRODUCTION

Non-islet-cell Tumor Hypoglycemia (NICTH) is a rare and challenging paraneoplastic syndrome that may accompany both benign and malignant nonpancreatic tumors [1]. It was first described in 1929 in a patient with hepatocellular carcinoma [2]; in 1930, a surgeon named Karl Walter Doege and a radiologist named Roy Pilling Potter separately reported two cases of pleural tumors in patients with symptoms of hypoglycemia [3, 4]. Since then the epoynm Doege-Potter Syndrome (DPS) has been used to describe cases of NICTH associated with a solitary fibrous tumor of pleura, secreting an abnormal and incompletely processed form of Insulin-like Growth Factor 2 (IGF-2) [1]. This syndrome is potentially life-threatening, and its diagnosis and management must be handled with care. To the best of our knowledge, approximately 290 cases of NICTH have been reported in the last 25 years [5], with solitary fibrous tumor being the most common reported histotype, described in 64 patients (22%) in whom the pleura was the main origin of the tumor (72%). To the best of our knowledge, this is the first case recorded in our university hospital. Interestingly, although mesenchimal tumors are the most common non-islet-cell tumor associated with paraneoplastic hypoglycemia, with symptoms of hypoglycemia [3, 4]. Since then the epoynm Doege-Potter Syndrome (DPS) has been used to describe cases of NICTH associated with a solitary fibrous tumor of pleura, secreting an abnormal and incompletely processed form of Insulin-like Growth Factor 2 (IGF-2) [1]. This syndrome is potentially life-threatening, and its diagnosis and management must be handled with care. To the best of our knowledge, approximately 290 cases of NICTH have been reported in the last 25 years [5], with solitary fibrous tumor being the most common reported histotype, described in 64 patients (22%) in whom the pleura was the main origin of the tumor (72%). To the best of our knowledge, this is the first case recorded in our university hospital. Interestingly, although mesenchimal tumors are the most common non-islet-cell tumor associated with paraneoplastic hypoglycemia,
mia, only 5% of pleural solitary fibrous tumors are estimated to result in NICHT. The reported age of patients with NICHT ranges from 5 to 94 years, with only one case of NICHT found in a 94-year-old man with a large pelvic fibrosarcoma [6]. In this report we describe the oldest patient with an uncommon case of paraneoplastic hypoglycemia discovered, present in a 96-year-old woman with NICHT secondary to a massive solitary fibrous tumor of the pleura.

2. CASE REPORT

A 96-year-old Caucasian woman was admitted to our institution after having experienced an unexplained fall accompanied by head trauma. In the emergency room the patient was found to have low capillary blood glucose (57 mg/dL), so intravenous boluses of 33% dextrose and infusion of 5% dextrose were administered to correct her hypoglycemia. She had a history of hypertension, cholecystectomy and two falls without fractures in the last two years. Medications included beta-blockers and platelet antaggregants. The patient had been in good health until approximately 1 year before admission, when she experienced a significant unintentional weight loss of 15 kg. Before hospitalization she was still independent in basic activities of daily living (Katz’s ADL [7] score = 5/6) but was partially dependent in instrumental activities related to daily living (Lawton’s IADL [8] score = 2/8). She was able to walk autonomously at home and with support while outside. No evidence of delirium emerged from screening using the 4AT test [9, 10]. Despite the advanced age, no overt cognitive deterioration emerged from the Mini-Mental State Examination. No overt cognitive deterioration emerged from the Mini-Mental State Examination (MMSE score = 24) [11]. Her physical examination showed that she was 165 cm tall and weighed 65 kg with a body mass index of 23.8 kg/m²; the Mini-Nutritional Assessment (MNA) [12] scored 6/14, suggesting overt malnutrition. Her body temperature was 36.5°C; her blood pressure was 130/70 mmHg; her heart rate was 80 beats per minute, while the respiratory rate was 18 breaths per minute (normal range for adults: 12-20 breaths per minute); oxygen saturation was 91% while breathing ambient air with a reduced lung murmur and dullness in the left hemithorax. On the left side of her face there was a 2-cm area of periorbital ecchymosis. The results of a standard electrocardiogram were reportedly normal. Computed Tomography (CT) of the head revealed a left orbital floor fracture with hematoma of the left jawbone sinus and a comminuted fracture of the ascending ramus of the right jaw. The temporomandibular joint evaluation showed a functional reduction in mouth opening. According to the findings of a surgical evaluation, a conservative approach was chosen, a soft diet was recommended, and analgesics and antibiotics were prescribed. Upon hospitalization, she continued to experience episodes of spontaneous hypoglycemia ranging from 30-50 mg/dL, requiring intravenous infusions of 10% dextrose with intravenous boluses of 33% dextrose. During her hospital stay she was provided with a 1600-kcal meal, divided into six equal portions daily. Other episodes of hypoglycemia as low as 35 mg/dL were recorded when the infusion drip rate was decreased. Laboratory work-up revealed normal liver and kidney function. Basal hormone analysis ruled-out the hypothesis of hypothyroidism and hy-nopoadrenalism. During a further hypoglycemic episode (<55 mg/dL), serum levels of insulin and c-peptide were suppressed, the concentration of IGF-1 was slightly reduced, and the total concentration of IGF-2 was within normal range. In light of her apparent hypoinsulinemic-hypoglycemia, an assessment of IGF-1/IGF-2 molar ratio (18.4) that widely exceeded the normal value of 3:1 was of great diagnostic value, ultimately indicating the presence of a Big-IGF-2 secreting non-islet-cell tumor (Table 1).

Table 1. Laboratory parameters: Normal ranges in parentheses.

| Blood Tests      | Values | Reference Ranges |
|------------------|--------|------------------|
| Glucose (mg/dl)  | 36     | 70-100 mg/dl     |
| Creatinine (mg/dl)| 0.7   | 0.5-0.9 mg/dl    |
| AST (U/l)        | 13     | <32 U/l          |
| ALT (U/l)        | 13     | <33 U/l          |
| Albumin (g/dl)   | 3      | 3.4-4.8 g/dl     |
| Alkaline phosphatase (U/l) | 79 | 35-104 U/l       |
| TSH (µU/ml)      | 3.7    | 0.27-4.2 µU/ml   |
| FT4 (pg/ml)      | 13.3   | 9.3-17.1 pg/ml   |
| Cortisol 8am (mcg/dl) | 7.54 | 6.24-18 mcg/dl   |
| Insulin (µU/ml)  | 0.1    | 2.6-24 µU/ml     |
| c-peptide (ng/ml)| 0.2    | 1.1-4.4 ng/ml    |
| IGF1 (ng/ml)     | 25.4   | 29-204 ng/ml     |
| IGF2 (ng/ml)     | 870    | 200-1000 ng/ml   |
| IGF2:IGF1        | 34.2   | <3               |
| Sodium (mEq/l)   | 143    | 135-145 mEq/l    |
| Potassium (mEq/l)| 3.7    | 3.4-4.8 mEq/l    |
| Hb (g/dl)        | 14.3   | 12-16 g/dl       |
| ph               | 7.42   | 7.33-7.43        |
| Bicarbonate (mmol/l)| 25.4 | 23-27 mmol/l    |
| Urinary Ketones  | Absent | Absent           |

Abnormal values are marked with bold.
FT4: Free Thyroxin; TSH: Thyroid Stimulation Hormone; IGF1: Insulin-Like Growth Factor 1; IGF2: Insulin-Like Growth Factor 2; Hb: Hemoglobin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase.

Chest X-rays showed that there was a space-occupying lesion in the left lower hemithorax with a significantly raised left hemidiaphragm (Fig. 1). A contrast-enhanced thoracoabdominal CT revealed a large pleural mass measuring 15.3 x 14 cm in the left lower hemithorax with compression of adjacent structures of the left mediastinum resulting in a complete atelectasia of lung parenchyma. No secondary lesions or pathological lymphadenopathy were described (Fig. 2A, B). A CT-guided percutaneous needle biopsy and subsequent histological analysis of the mass were performed. Histological findings included cell proliferation consisting of
fused elements arranged in differently oriented bundles with mild nuclear atypia, as well as variable cell density with areas of hypercellularity and focal hemangioperictoma-like aspects. Mitosis and necrosis were not present. Immunohistochemistry revealed that the tissue was positive for STAT6 and negative for WT-1, CK-AE1/AE3, Actine, S100, and Ki67, confirming the diagnosis of a solitary fibrous pleural tumor. Based on these findings, a diagnosis of DPS was confirmed. Considering age, large tumor burden, local disease extension, and an elevated surgery risk, the tumor was deemed unresectable and a conservative approach was chosen. In order to prevent serious hypoglycemic episodes while weaning the patient off of continuous glucose infusion, steroid therapy with IV dexamethasone 8 mg daily was started. On this regimen she was able to maintain stable euglycemic control with capillary blood glucose levels remaining between 90-130 mg/dL (Fig. 3). Dexamethasone was reduced to 4 mg once daily per os, and dextrose infusion was successfully decreased and then finally discontinued 3 days after starting steroid therapy. The patient was then discharged from the hospital with only oral therapy. For more than 5 months she fared well at home, living without hypoglycemic episodes up until her next follow-up visit.

Fig. (1). Anteroposterior view chest X-ray showing a space-occupying lesion in the left lower hemithorax with a significantly raised left hemidiaphragm.

Fig. (2). Computed tomography of the thorax and abdomen showed a large mass in the left hemithorax – A) sagittal view, B) horizontal view.

Fig. (3). Capillary blood glucose follow-up at 12-hour intervals in response to dextrose infusion and glucocorticoid therapy (Dexamethasone 8mg daily). Dotted line indicates capillary blood glucose value at lower end of normal (70 mg/dl).
3. DISCUSSION

Hypoglycemia is one of the most common medical emergencies. The acute consequences of hypoglycemia have detrimental effects on older people who already have an increased risk of suffering from fall-related complications such as head trauma or bone fractures. Clinicians should be aware of hypoglycemia as a possible cause of sudden and unexplained falls, especially in older frail patients. Although most episodes of recurrent hypoglycemia are secondary to hypoglycemic therapy used to treat diabetes mellitus, rare cases can be a manifestation of neoplastic diseases. Apart from endogenous hyperinsulinism due to pancreatic islet B-cell tumors (insulinoma), spontaneous hypoglycemia is sometimes the result of a paraneoplastic syndrome caused by non-pancreatic tumors and it is known as Non-Islet Cell Tumor Hypoglycemia (NICTH). A wide variety of malignant and benign tumors may cause NICTH. According to Bodnar [13], there are nearly 290 cases of NICTH that have been reported thus far, with most of the literature reporting mesenchimal tumors such as Solitary Fibrous Tumors (SFT) and hemangiopericytoma. On the other hand, tumors of nonmesenchimal origins are much less commonly reported and described. SFTs are usually large tumors that often derive from pleura but may also occur in many visceral sites, such as in the abdominal cavity or retroperitoneum. Typically, they are well differentiated and slow growing cancers, with a size usually exceeding 10 cm. Most of them are generally associated with a good prognosis, with local recurrences occasionally described; distant metastases have been reported, albeit rarely, in up to 15% of cases. Because of these features, symptoms usually appear late in the clinical course as a result of compression of nearby vital structures. Additionally, any one of a number of paraneoplastic syndromes may comprise the first clinical manifestation of a SFT. Seborrheic Keratosi, hypokalemia, hyperkalemia, Pierre Marie hypertrophic arthropathy, and hypoglycemia have all been reported as syndromes associated with benign and malignant SFTs [14]. Notably, although pleural SFTs are now regarded as the second most common cause of paraneoplastic hypoglycemia, referred to as Doege-Potter Syndrome (DPS), only 5% of all cases reporting SFT thus far have been associated with spontaneous hypoglycemia [15]. In a study by Meng et al. [5], DPS was concluded to be a very rare syndrome, with only 45 cases reported since 1979 and with patients ranging from 38 to 79 years of age. To the best of our knowledge, there has been only one other case of NICTH reported in a patient older than 90 years of age. The patient, described by Alharbi [6], was a 94-year-old man suffering from paraneoplastic hypoglycemia due to a large pelvic fibrosarcoma. In our paper, we describe a 96-year-old woman who presented with head trauma following an unexplained fall that likely occurred because of hypoglycemia caused by a pleural SFT. In our case, the diagnosis of NICTH was made on the basis of low insulin and C-peptide levels (less than <3 μU/mL and less than 0.6 ng/mL, respectively) without ketoacidosis, suggesting a high insulin-like hypoglycemic effect, a hallmark of paraneoplastic disease in non-islet-cell tumors. Anti-insulin antibodies were not measured in the first place, but even if present, they would not explain hypoglycemia in the presence of low levels of insulin. Generally, an aberrant secretion of an incompletely processed form of IGF-2 referred to as Big IGF-2 is considered the main cause of enhanced insulin-like activity in patients with NICTH [16]. In normal serum, about 80% of the circulating IGF-2 forms a stable 150 kDa ternary complex with Insulin-Growth Factor Binding Protein 3 (IGFBP-3) and an Acid Labile Subunit (ALS). This large complex then effectively traps IGF-1 and IGF-2 proteins in the vascular space, protects them from degradation, limits their binding to receptors, and maintains a ‘reservoir’ of biologically inactive IGF [17]. On the contrary, steric hindrance of big IGF-2 prevents the proper formation of this ternary complex, leading to a smaller binary complex with a greater capillary permeability. Accordingly, the bioavailability of IGF-2 increases in target tissues because more IGF-2 crosses capillary walls. Due to the fact that IGF-2 has structural homology with insulin, IGF-2 is able to promote hypoglycemia by inhibiting glycogenolysis, gluconeogenesis, and by enhancing peripheral glucose uptake by mainly skeletal muscle. Finally, the activation of insulin receptors leads to the suppression of ketogenesis and decreases free fatty acid release. Moreover, the excess of Big IGF-2 is thought to displace IGFs from IGFBPs. As a consequence, a relatively higher amount of free-IGF-1 (the bioactive form of IGF-1) negatively feeds back to inhibit GH release, leading to further impairment of the ternary complex by down-regulation of the GH-dependent proteins IGF-1, IGFBP, and ALS. The effects of tumor-induced Big IGF-2 therefore amplify progressively, increasing IGF-2 bioavailability, while simultaneously rendering patient tissue more and more vulnerable to the effects of NICTH.

Our data confirmed that hypoglycemia resulting from the patient’s pleural SFT may have been related primarily to the upregulation of Big IGF-2. Even if IGF-2 levels were normal, IGF-1 levels were suppressed under 30 ng/mL, meaning that the IGF-2:IGF-1 ratio was elevated above the normal cut-off of 3:1. Although the radioimmunoassay method used did not discriminate between Big IGF-2 and normal IGF-2, the high IGF-2:IGF-1 ratio was strongly consistent with the hypothesis of DPS.

On the basis of NICTH pathogenesis, an IGF-2:IGF-1 ratio exceeding 10:1 is considered to be an important screening tool for NICTH. As is commonly reported, the measurement of the total IGF-2 concentration is not an accurate diagnostic tool because nearly half of the patients with NICTH show normal IGF-2 levels. Moreover, measuring Big IGF-2 is a cumbersome and time-consuming procedure. Size-exclusion acid chromatography and Western-blot analytical procedures have been proposed [18], but commercial assays for Big IGF-2 are not available.

Treatment of DPS typically involves surgical removal of the mass, usually resulting in a complete resolution of hypoglycemia. When total resection is not possible, partial resection, as well as tumor embolization, radiation therapy, or chemotherapy should be considered and selected based on histopathology of the tumor. In our case, because of advanced patient age and large tumor burden, resection was not feasible. In this setting there is no standard of care. However, the administration of glucocorticoids and an increased intake of carbohydrates have proven to be effective in managing this syndrome [19-23]. While receiving glucocorticoid therapy, several mechanisms including an increase in hepatic...
growth hormone to increase levels of IGF-binding protein approaches include the off-label use of recombinant human analogues, as these therapies have not been shown to be effective in treating NICTH because hypoglycemia is not mediated by endogenous insulin. Other reported treatment approaches include the off-label use of recombinant human growth hormone to increase levels of IGF-binding protein and ALS, thereby restoring the ternary complex that binds IGF-2, ultimately decreasing IGF-2 bioavailability [24-27]. Furthermore, although long-term GH treatment may be helpful in alleviating hypoglycemia, its beneficial effects are diminished by potential side effects, especially in older patients. High costs and concerns about tumor progression limit the effectiveness of GH treatment because of possible mitogenic effects.

CONCLUSION

In conclusion, DPS is an uncommon paraneoplastic syndrome associated with a solitary fibrous tumor, characterized by severe hypoglycemia and a consequently higher risk of falls, especially in the elderly. The most likely mechanism to explain hypoglycemic episodes is an overproduction of an incompletely processed precursor of IGF2, referred to as Big IGF-2, which is able to exert strong insulin-like hypoglycemic effects on target tissues. Prompt and total surgical resection is curative. If resection is not feasible, as in the case of our patient, glucocorticoid administration accompanied by an increase in caloric intake are effective in alleviating and preventing hypoglycemia, and ultimately in treating NICTH.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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