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Hypoglycemia as a sign of paraneoplastic syndrome in a patient with pleural fibroma

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Summary. Paraneoplastic syndrome has a wide range of symptoms and fasting hypoglycemia is one of its possible clinical manifestations. It is mostly caused by insulinomas and non-islet cell tumors (large mesenchymal tumors account for more than a half of all neoplasms associated with hypoglycemia). Clinical features may vary and typical laboratory features of paraneoplastic hypoglycemia include a low level of fasting glucose and C-peptide, low insulin growth factor 1 (IGF1) and elevated levels of "big" insulin growth factor 2 (IGF2). The increased IGF2: IGF1 ratio is considered to be pathognomic for this diagnosis. Although paraneoplastic hypoglycemia is mostly present in patients with an already diagnosed malignancy, this eventuality should be considered in patients having unclear and inexplicable hypoglycemia. Proper treatment can significantly reduce the symptoms and improve the quality of life.

Key words: hypoglycemia, insulin growth factor 2, non-islet cell tumors, paraneoplastic syndrome, therapy

«L'ipoglicemia come sintomo di sindrome paraneoplastica in un paziente con fibroma pleurico»

Riassunto. La sindrome paraneoplastica presenta una vasta gamma di sintomi e l'ipoglicemia da digiuno è una delle sue possibili manifestazioni cliniche. Questa manifestazione è causata principalmente da insulinoma e da tumori non-insulari (più della metà di tutti i tumori associati a ipoglicemia sono rappresentati da grandi tumori mesenchimali). Le caratteristiche cliniche possono variare e le caratteristiche tipiche della ipoglicemia paraneoplastica riscontrate in laboratorio, comprendono bassi livelli di glucosio a digiuno e di peptide C, bassi livelli del fattore di crescita insulinico-1 (IGF1) ed elevati livelli del fattore di crescita "big" insulino-2 (IGF2). L'aumento del rapporto tra IGF2 e IGF1 è considerato patognomonico di questa diagnosi. Anche se l'ipoglicemia paraneoplastica è presente soprattutto in pazienti a cui è stata già diagnostica una patologia maligna, è necessario prendere in considerazione questa eventualità anche in pazienti che presentano una non chiara ed inspiegabile ipoglicemia. Un trattamento adeguato può significativamente ridurre i sintomi e migliorare la qualità della vita.

Parole chiave: ipoglicemia, fattore di crescita insulinico-2, tumori non insulari, sindrome paraneoplastica, terapia

Introduction

Paraneoplastic hypoglycemia (PH) occurs as a relatively rare manifestation of cancer. Several types of tumor manifesting by hypoglycemia have been described among non-islet cell tumors (NICT). More than half of them comprise large mesenchymal tumors localized mainly in the retroperitoneum and pelvic areas (65%) or chest (30%). Epithelial tumors represent less than 0.1 %.

Gastrointestinal stromal tumors (GIST) are often associated with hypoglycemia, too. The most com-

mon appearance of GIST is in the stomach (60-70%), followed by the small intestine, colon and rectum (1). GIST rarely manifest as pelvic masses (2). The gynecological tumors associated with hypoglycemia are particularly leiomyosarcoma, solitary fibrous tumor and fibrosarcoma (3). Others include mesothelioma, hemangiopericytoma, solitary fibrous tumors, fibrosarcomas, synovial sarcoma, myxoid liposarcoma, chondrosarcoma, Ewing's sarcoma and undifferentiated pleiomorphic sarcoma.

Hypoglycemia may sometimes also be a symptom of fibrous tumor of the pleura (FTP), the incidence being approximately 5% of cases (4). Doege and Potter were the first to describe this phenomenon in association with intrathoracic tumors in 1930 - Doege-Potter syndrome (5, 6). Hypoglycemia usually appears in tumors located on the right sight of the chest and in malignant forms of fibrous tumor of the pleura with a diameter of more than 10 cm. The occurrence of hypoglycemia is three times more likely in women (7).

Among primary epithelial tumors, episodes of hypoglycemia have been described in patients with large cell adenocarcinoma, hepatocellular carcinoma, renal cell carcinoma, phyllodes tumor of the breast and ovarian adenocarcinoma.

An overview of non-islet cell tumors associated with paraneoplastic manifestations of hypoglycemia is presented in Table 1. Some episodes of paraneoplastic hypoglycemia are closely connected with the metastatic spread of the tumor itself and these are characterized by an increased level of insulin-like growth factor IGF1 and normal levels of IGF2 (8).

Symptoms of hypoglycemia include andrenergic and neuroglycopenic symptoms. Andrenergic symptoms stem from perception of physiologic changes caused by the autonomic nervous system's response to hypoglycemia. Neuroglycopenic symptoms derive from low-level glucose supply through cerebral shortage (Table 2).

Table 1. Overview of non-islet cell tumors associated with paraneoplastic manifestations of hypoglycemia (1, 4, 20).

Mesenchymal tumors	Epithelial tumors
Gastrointestinal stromal tumors	hepatocellular carcinoma
Myxoid liposarcoma	large cell adenocarcinoma
Leiomyosarcoma	adenocarcinoma of the ovary
Solitary fibrous tumor	phyllodes tumor of the breast
Fibrosarcoma	renal cell carcinoma
Mesothelioma	
Hemangiopericytoma	
Chondrosarcoma	
Ewing's sarcoma	
Pleomorphic undifferentiated sarcoma	
Synovial sarcomas	
Multiple myeloma *	

* The mechanism responsible for the occurrence of hypoglycemia in multiple myeloma is autoimmune insulin syndrome.

Pathogenesis

The etiopathogenesis of hypoglycemia in patients suffering from non-islet cell tumors includes destruction of insulin or insulin receptors by infiltrative tumor growth and excessive utilization of glucose due to increased secretion of insulin growth factor prohormone 2 (IGF2) named "big IGF2" (9).

IGF2 gene is overexpressed in neoplastic tissues. This is followed by excessive production of IGF2 prohormone ("big IGF2") that binds to the insulin receptor and the receptor for insulin growth factor in the liver and muscle). The result is a decrease in the production of glucose and increased utilization of glucose in peripheral tissues (10). Total IGF2 level may be normal but the elevated level of prohormone IGF2 is important from a diagnostic perspective while the ratio of IGF2: IGF1 (which is increased) should also be considered (11). The secretion of insulin and growth hormone is inhibited by the higher concentrations of IGF2. It results in a decrease in circulating complexes of IGF1 and IGF-binding protein-3 (12). The consequence of these changes is a low level of fasting glucose in the serum accompanied by low levels of proinsulin, insulin (IRI, less than 4.0 uU/ml, C-peptide less than 0.1 ng/ml), growth hormone below 0.1 ng/ml and IGF1 factor (normal range: 46-284 ng/ml), as well as elevated levels of "big IGF2" (normal range IGF2 and

Table 2. Symptoms of hypoglycemia (19).

General symptoms	nausea, dizziness, collapse, weight gain
Andrenergic symptoms	sweating, tremor, palpitations, tachycardia, agitation, nervous excitability, hunger
Neuroglycopenic symptoms	confusion, impairment of consciousness, mental concentration, sensation of warmth, weakness or fatigue, severe cognitive failure, seizure, coma

IGF2 precursor: 28-444 ng/ml) and an increased IGF2 : IGF1 ratio (more than 10 : 1). The IGF2 : IGF1 ratio is mostly evaluated by chromatographic methods and is considered to be pathognomic for this diagnosis.

Treatment

The most important therapeutic intervention in patients suffering from paraneoplastic hypoglycemia is treatment of the primary tumor itself (mostly by surgical intervention followed by adjuvant chemotherapy or radiotherapy). In those having no benefit from surgical treatment or in patients with tumors unsuitable for resection, symptomatic treatment is indicated (13).

To manage acute hypoglycemia one mainly needs continuous administration of 10 % glucose solution. Other potential treatment options include intramuscular or intravenous administration of glucagone, corticosteroids, human growth hormone or potent inhibitor of insulin secretion, diazoxid/hydrochlorothiazide (14). Again, successful administration of imatinib (tyrosine kinase inhibitor) has been described in patients suffering from gastrointestinal stromal tumors, and likewise administration of IGF1 antagonist in Ewing's sarcoma.

Case report

We report on a 76 year-old women with pleural fibroma which was diagnosed by chest X-ray examination as part of a preventive medical examination in 2000 (Fig. 1). A computed tomography was then performed and a peripheral tumor (suspect fibroma l.sin.) was detected. The patient did not have any complaints or clinical symptoms at that time. She underwent fibrobronchoscopy – no tumorous changes of the tissue were seen, and cytological and histological examination did not reveal any malignant cells.

In August 2000 peripheral wedge resection of the tumor was performed via left lobe videothoracoscopy. After histological examination the conclusion was fibrous tumor of the pleura. The patient did not receive any other treatment and was monitored only by her general practitioner.

In 2006 a breast tumor was ascertained by ultrasound during a gynecological examination. Right segmental mastectomy and extirpation of six axillary lymph-nodes were performed (histologically moderately differentiated invasive breast carcinoma). Our patient, however, did not follow the recommended treatment and follow-up.

First in July 2007 exertional dyspnea and sweating appeared. Computed tomography of the chest was again performed and two suspect fibromas on the

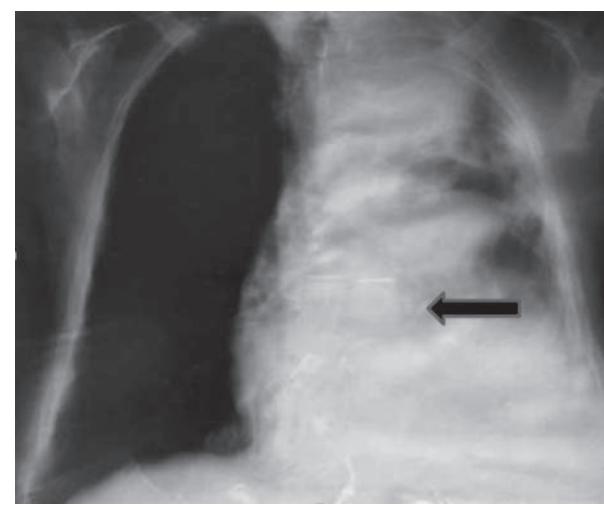

Figure 1. Chest X-ray – non-homogenous shadowing of the left lung.

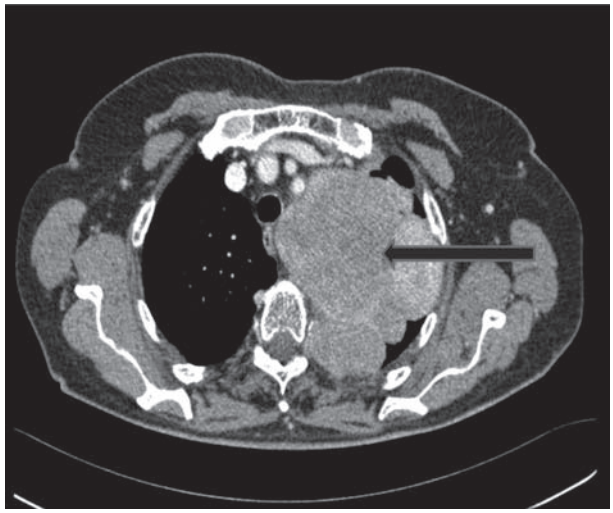

Figure 2. Computed tomography of the chest – multifocal tumors in the whole left hemithorax (horizontal).

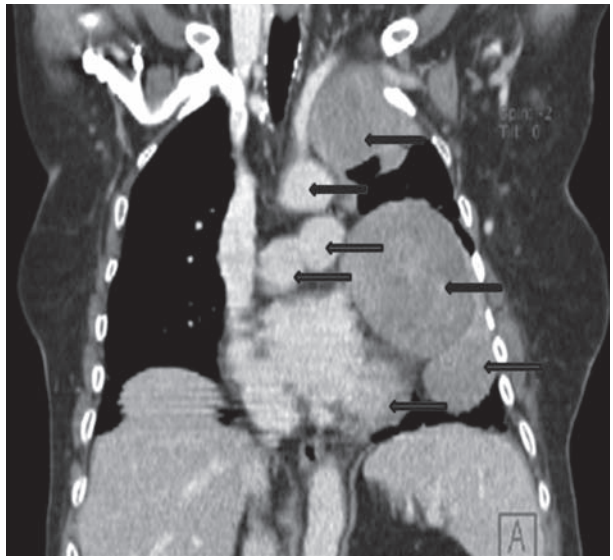

Figure 3. Computed tomography of the chest – multifocal tumors in the whole left hemithorax (vertical).

lateral side of the left hemithorax were found (Figs. 2, 3). However, fibrobronchoscopy did not reveal any signs of cancer. The patient underwent left axial thoracotomy and extirpation of seven infiltrates of the left chest wall and one infiltrate of mediastinal pleura. A histologically highly infiltrative and hypercellular tumor formed from spindle cells was detected (without significant cytologic atypia and with no signs of necrosis, its mitotic activity exceeding 4 mf/10 HPF). According to the immunohistochemical analysis, the tumor cells were positive for vimentin, CD34, CD99 and bcl-2 and negative for CK 7, CK 8/18, EMA and calretinin. Proliferative activity (Ki-67 index) was about 20-30%. The above description corresponds to a solitary malignant pleural fibroma.

Our patient again refused the treatment recommended. In March 2009 we remarked a relapse of solitary fibrous tumor of the pleura with multiple metastases to the mediastinal parietal pleura and left lung. Clinically dyspnea upon minimal exertion was the dominant feature. Because of the stage of the tumor, surgical treatment was not indicated. In the following months we noted progression and proliferation of the tumor. We found growth of pleural metastases accompanied by overgrowth of the neuroforamina and thoracic vertebrae Th2 - Th3 as well as slight oppression of the mediastinal structures and the heart.

In August 2011 our patient was hospitalized with the diagnosis of short-term unconsciousness early in the morning. During examination at the Emergency Department extremely low levels of blood glucose were detected (1.0 mmol/L). A solution of 40% glucose (40 ml) was administered intravenously leading to gradual recovery of consciousness (blood glucose 12.3 mmol/L). During the next three days of hospitalization symptomatic fasting hypoglycemia occurred repeatedly. The minimal level of glycemia (1.3 mmol/L) was accompanied by adrenergic warning symptoms (sweating, tachycardia) without any qualitative or quantitative changes of consciousness. Continuous intravenous glucose solution was administered. However, the glucose infusions were only administered at the beginning of treatment for the short period of time, which is why we did not expect severe adverse effects including growth of the primary tumor.

The main clinical symptom was dyspnea upon minimal exertion (without chest pain or hemoptysis, and no cough). Manifestations of irritation of the cervical sympathetic trunk and features of Claude-Bernard-Horner syndrome were present. After overnight fasting symptomatic hypoglycemia was again confirmed (fasting glycemia 0.3 mmol/L, IRI 0.00 uU/ml and C-peptide 0.066 ng/ml). We examined the IGF1 (29.41 ng/ml; range 46-284 ng/ml). The level of IGF2 was not examined since the test was unavailable

in the lab. The one and only adrenergic symptom during the episodes of hypoglycemia was sweating, while the main neuroglycopenic expression was somnolence.

Based on these clinical and laboratory features we considered the hypoglycemia to be a secondary (paraneoplastic) symptom of the malignancy. We considered reducing the tumor mass and its metabolism and consulted the oncologists about palliative chemotherapy. But because of the extent of the disease this was not indicated. We initiated corticosteroid therapy at a dose of 16 mg per day, first in one dose, later divided into three doses per day (8-4-4 mg).

Administration of corticosteroids lasted for one year, during which we recorded a slight increase in weight (about 3 kg, previous weight gain since diagnosis of malignancy having been about 10 kg per year). During this treatment the patient was without any recurrence of hypoglycemia and among the possible adverse effects of this treatment we recognized only worsening of osteoporosis.

The patient refused any oncological or surgical treatment and died of her primary oncologic diagnosis 13 months after the start of corticotherapy.

Discussion

Paraneoplastic hypoglycemia is a rare symptom of any type of cancer. In many patients suffering from paraneoplastic hypoglycemia the cancer is already known and is mostly characterized by the advanced stage of the disease. But in some cases it may be the first clinical manifestation of the tumor. Hence it is necessary to bear this in mind as a possibility in those having unclear and inexplicable hypoglycemia.

One of the main characteristic features of paraneoplastic hypoglycemia is severe persistent fasting hypoglycemia which requires continual intravenous administration of glucose solutions. Due to the fact that the onset of fasting hypoglycemia is usually gradual, vegetative symptoms are rare or absent and in most patients we can more often recognize only neuroglycopenic symptoms.

Differential diagnosis includes all other conditions that can cause fasting hypoglycemia, especially kidney or liver failure, adrenal insufficiency, sepsis, pancreatic B-cell tumors, ingestion of alcohol or drugs (mostly insulin or oral antidiabetic agents) (15, 16). Most of these conditions may be excluded relatively easily and a broader examination usually involves only B-cell tumors of the pancreas, non-islet cell tumors or adrenal impairment.

However, in differential diagnosis of paraneoplastic hypoglycemia one should not forget that rare reason for hypoglycemia – monoclonal gammopathy. The mechanism responsible for its appearance is insulin autoimmune syndrome (AIS) which is rare in Europe but quite common in Japan (where it is the third most common cause of hypoglycemia after insulinoma and hypoglycemia associated with NICT). Outside Asia 58 reports of autoimmune hypoglycemia have been described (mostly in patients with multiple myeloma – plasmocytoma) (17). AIS can easily be confused with insulinoma because of its similar clinical features. Only the examination of (auto)antibodies against insulin (in patients who have never had an exogenous insulin) or autoantibodies against insulin receptor may reveal the correct diagnosis. Unlike hypoglycemia associated with non-islet cell tumors and insulinomas, AIS may be accompanied not only by fasting hypoglycemia but also by reactive postprandial hypoglycemia (18). Clinical and laboratory features of hypoglycemia associated with non-islet cell tumors, insulinoma and AIS are described in table 3. As this type of hypoglycemia is often secondary to preexisting disease (already diagnosed), antibody screening is not always necessary (19, 20).

The treatment of this rare cause of hypoglycemia is challenging. These patients require continual administration of glucose to maintain euglycemia and to reveal symptoms of hypoglycemia. Our patient suffered from hypoglycemia for more than 6 weeks before any adequate treatment started. Another treatment option is corticosteroids although several possible adverse effects of such treatment should be considered. However, in patients suffering from a complication such as malignant disease the benefit from this treatment outweighs the risk of adverse effects and it may be considered a life-saving treatment.

The major benefit in terms of maintaining sustained euglycemia is that the patient does not need continuous intravenous administration of glucose. From a therapeutic angle the dose and timing of the treatment

Table 3. Clinical and biochemical characteristics of hypoglycemia in patients with NICT1, insulinomas and autoimmune hypoglycemia.

Signs	NICT	Insulinoma	Autoimmune hypoglycemia
Hypoglycemia	Fasting	Fasting*	Fasting and postprandial
72 hour fasting test	Positive	Positive	Variable
Insulin	Low	High	Very high
C-peptide	Low	High	Very high
Proinsulin	Low	High	Very high
Sulfonylurea in plasma	Negative	Negative	Negative
Insulin antibodies or insulin receptor antibodies	Negative	Negative	Positive
E-domain (big) IGF2[2]	Positive	Negative	Negative
Imaging	Positive	Positive	Negative
Association with diseases	The most common mesenchymal tumors	Multiple endocrine neoplasia type 1 (MEN type 1)	Hematologic and rheumatologic diseases, drug-induced

1 non-islet cell tumor
2 insulin-like growth factor 2
* In extreme cases insulinomas are also associated with postprandial hypoglycemia

are likewise important – in our patients a single dose of corticosteroids was not effective: only by dividing it into three doses per day were we able to maintain euglycemic levels of blood glucose. When there is the possibility of specific treatment, it should start as soon as possible (e.g. administration of imatinibe - tyrosine-kinase inhibitor in gastrointestinal stromal tumors). In some patients diazoxide (a potent inhibitor of insulin secretion) may also be used. Surgical treatment can be effective especially in patients suffering from slowly growing mesenchymal tumors.

In most patients, however the results are often poor because of the size and grade of the tumor itself.

Conclusion

As the incidence of cancer grows all over the world, we nowadays see symptoms of paraneoplastic syndrome more often. Paraneoplastic hypoglycemia is one of a wide range of such symptoms and - more important - proper treatment may significantly improve the quality of life in cancer sufferers.

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