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Case Report

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Primary malignant fibrous histiocytoma of the lung: IGF-II producing tumor induces fasting hypoglycemia

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Summary: Augmented glucose utilisation or secretion of insulin-like-growth-factor II (IGF-II) are discussed as important pathogenetic factors in tumor-associated hypoglycemia (Doege-Potter Syndrome) with suppressed insulin and C-peptide levels. Primary malignant fibrous histiocytoma of the lung is an uncommon neoplasia and its association with hypoglycemia is rare and the causal relationship remains unclear. – We report a 57-year-old male with spontaneous hypoglycemia (1.67 mmol/l) due to a primary malignant fibrous histiocytoma of the lung, secreting IGF-II. Insulin (0.10 nmol/l; normal range 0.33–1.2) and C-peptide (3.0 mIU/l; 5–25) levels were suppressed in combination with low levels of growth hormone (<0.5 ng/ml; <7 ng/ml) and IGF-I (<66.0 ng/ml; 70–246). The elevated IGF-II level (787 ng/ml; 300–500) and decreased IGF-binding protein 3 (1.6 mg/l; 2–5) indicated a high free IGF-II activity. After surgery (resection of the right upper lobe), glucose (4.4 mmol/l), insulin (9.0 mIU/L) and C-peptide (0.84 nmol/l) levels returned to normal. Serum IGF-I (289 ng/ml) and the IGF-I/IGF-II ratio (<0.08 preoperative vs. 0.41 postoperative; >0.20) increased to the normal reference range. – In conclusion, malignant fibrous histiocytoma (MFH) is rarely described presenting as tumor-induced hypoglycemia. Doege-Potter Syndrome in MFH seems to be related to tumor-associated IGF-II production.

Introduction

The association of tumors with hypoglycemia (Doege-Potter Syndrome) (Doege, 1930; Potter, 1930) is well documented but the pathogenesis of hypoglycemia in some non-islet cell tumor is still unclear (Chamberlain and Taggart, 2000; Teale and Marks, 1990). Two major causes of fasting hypoglycemia are associated with tumors: the insulin production by islet cell tumors and the production of hypoglycemia by extrapancreatic tumors (non-islet cell tumors) through other mechanisms. There are 3 mechanisms of hypoglycemia associated with non-islet cell tumors: insulin-like activity (e.g. IGF-II-producing tumors), glucose consumption by the neoplasm and failure of compensatory mechanisms such as pituitary insufficiency, adrenal insufficiency or hepatocellular dysfunction (Eastman and Kahn, 1990). Although the non-islet cell tumors may be clinically indistinguishable, distinctions often can be achieved by various laboratory studies and measurements. The tumors associated with hypoglycemia can be mesenchymal or epithelial in orgin (Enzinger et al., 1969), with 50% of the cases respectively. Mesenchymal tumors associated with hypoglycemia usually weigh more than 1 kg, are larger than 5 cm in diameter, and arise from fibroblasts, endothelial cells and myogenic cells.

Malignant fibrous histiocytoma is the most common soft tissue sarcoma in adults (Sato et al., 1996), but primary malignant fibrous histiocytoma of the lung is very rare (Halyard et al., 1996; Juetter et al., 1987; Lessel and Erbstosser, 1984) and only a few cases have been reported in the literature with tumor associated hypoglycemia (Doege-Potter Syndrome) (Vollmar and Wockel, 1977; Wasada et al., 1992). The present case clearly documentes a nonsuppressible insulin-like activity (NSILA-s) with tumor-inducing IGF-II production.

Case report

A 57-year-old male was admitted to the hospital after he had provoked a car accident. On admission, he remembered that while driving, he felt sweaty, hungry and had feelings of giddiness. Later, he had a retrograd amnesia. On the scene of the accident, he has been wandering around, speaking in the manner of a sensoric and motoric aphasia. On the

way to the hospital, venous plasma glucose was 1.67 mmol/l (3.89–5.55). The symptoms of hypoglycemia completely resolved after infusion of intravenous glucose. At this point no specific neurological abnormalities were detected. He reported that he had not eaten breakfast that morning. The patient could remember similar attacks during daytime over the previous months. After ingestion of meals, the symptoms were quickly regredient. Furthermore the patient (non-smoker) reported of increased frequency of irritable cough. During the following days, stabilization of plasma glucose levels required continuous infusion of intravenous glucose 40% (500 mg/24 h). The chest radiograph showed a large intrathoracic mass approximately one-third of the right hemithorax (Fig. 1 and 2). All other radiographs, including a cranial computed tomography, which excluded intracerebral bleeding, did not show any remarkable findings. The infusion was stopped for three hours under medical control and the symptoms of hypoglycemia returned. Blood glucose was measured by 2.3 mmol/l, C-peptide in serum less than 0.10 nmol/l (0.33–1.2), serum insulin less than 3.0 mIU/l (5–25). Results of thyroid and hepatic function tests were normal. Adrenal insufficiency could be excluded by ACTH-test. The tumor markers squamous cell carcinoma antigen (SCCA), neuron-specific enolase (NSE) and carcinoembryonic antigen (CEA) were normal. Hemoglobin was 15 g/dl, blood gas analysis was unremarkable.

Growth hormone (GH) was <0.5 ng/ml (<7 ng/ml), IGF-I was <66.0 ng/ml (70–246), IGF-II was 787 ng/ml (300–500), IGF-I to IGF-II ratio less than 0.08 (reference value, greater than 0.20), IGF-binding protein 3 (IGFBP-3) 1.6 mg/l (2–5). Surgical exploration revealed a huge non-encapsulated, yellow-grey tumor, measuring 13×8 cm of soft consistence that could be resected without pleurectomy. The histological examination showed an undifferentiated, cell rich tumor with mitosis in irregular distribution and allowed no histological classification (Fig. 3). The immunohistochemistry revealed clearly a malignant, fibrous histiocytoma (Table 1). After successful resection of the right upper lobe, IGF-II, IGFBP-3, glucose, insulin and C-peptide levels returned to normal (Table 2). Serum IGF-I (289 ng/ml) was

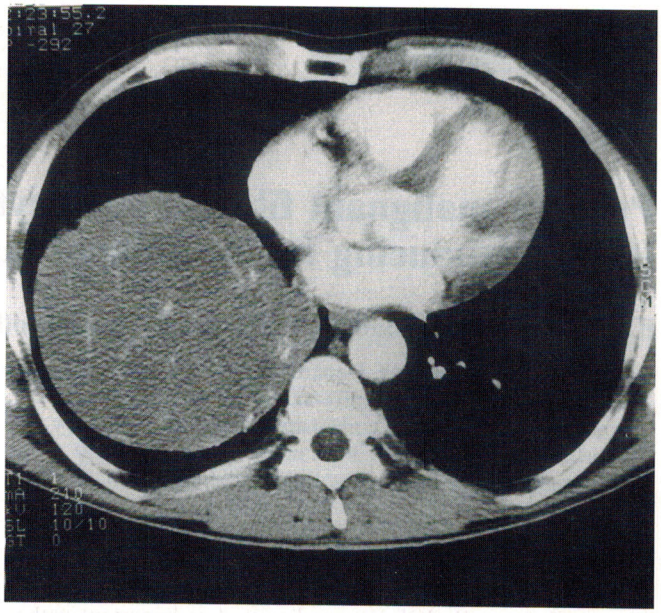

Fig. 2 Computed tomography of the thorax of a 57-year-old male with a malignant fibrous histiocytoma of the lung

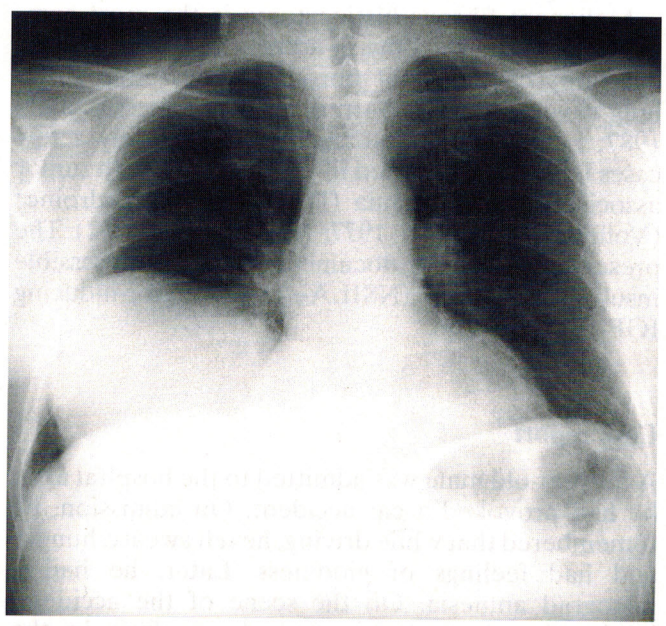

Fig. 1 X-ray of the chest (anterior-posterior) of a 57-year-old male with a malignant fibrous histiocytoma of the lung

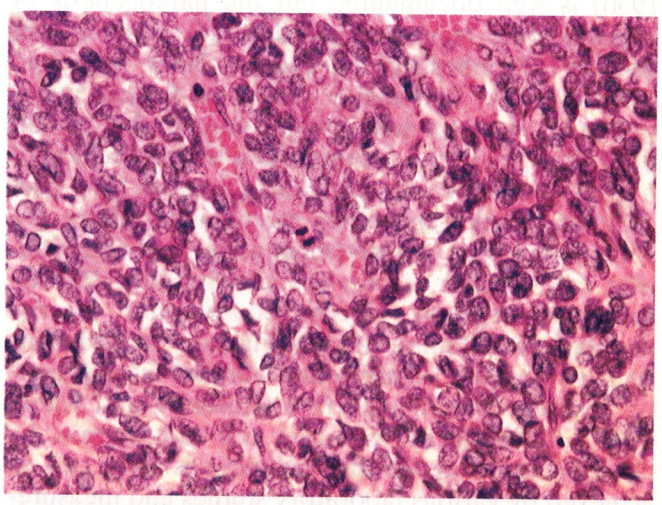

Fig. 3 Undifferentiated, cell rich tumor in the lung. Mitosis in irregular distribution. Tumor cells with great nuclei and loosely structured chromatin. Differentiation allows no histological classification. Immunohistochemistry reveals malignant fibrous histiocytoma

Table 1 Summary of immunhistiochemistry

Positive reaction:	alpha-1-antitrysin, vimentin
Negative reaction:	unspecific enulase, S-100-protein, cytoceratin, lysocym and factor 8

Table 2 Hormone levels and plasma glucose

	Preoperative	Postoperative	Normal range
Glucose (mmol/l)	1.67	4.40	3.89–5.55
C-peptide (nmol/l)	<0.10	0.84	0.33–1.22
Insulin (mIU/l)	3.0	9.0	5–25
GH (ng/ml)	<0.5	1.1	<7
IGF-I (ng/ml)	<66	289	70–246
IGF-II (ng/ml)	787	699	300–500
IGF-I/IGF-II	<0.08	0.41	>0.20
IGFBP-3 (mg/l)	1.6	3.2	2–5

slighly elevated. One year later, the patient is well without signs of tumor recurrence.

Discussion

The combination of fasting hypoglycemia and undetectable insulin and C-peptide levels led to the hypothesis of non-islet cell tumor induced hypoglycemia. Non-islet cell tumors of various types have been shown to produce insulin-like growth factors (e.g. IGF-II), in particular excessive quantities of high molecular weigh (big) IGF-II (Marks and Teale, 1993). IGF-II secretion by tumor is responsible for hypoglycemia by direct insulin-like action on non-hepatic tissues (Daughaday and Trivedi, 1992). Suppression of growth hormone (GH) from pituitary cells is most likely the result of high concentration of serum IGF-II because IGF-II inhibits the secretion of GH. The low level of serum IGF-I could be secondary to the suppression of GH, which is a major regulator in IGF-I production (Teale and Marks, 1990). The finding of low or suppressed IGF-I and inappropriately normal or elevated levels of IGF-II in patients with hypoglycemia is strong evidence for a nonislet-cell neoplasm (Dauhaday et al., 1988; Teale and Marks, 1990). The induction of hypoglycemia by excessive IGF-II production by non-islet cell seems to involve also alterations in the binding of IGF-II to the major circulating binding protein 3 (IGFBP-3) (Baxter and Daughaday, 1991). In the present case, reduced IGFBP-3 level is caused by suppressed GH level. The reduced GH level, in addition to affecting binding proteins, may explain increased sensitivity to the hypoglycemic action of IGF-II. Postoperatively, the total IGF-II level was still elevated (699 ng/ml; 300–500), free IGF-II fraction, however, has obviously been significantly reduced due to the increase in IGFBP-3 level. Furthermore GH, c-peptide, insulin and IGF-I/IGF-II ratio returned to normal. The intial inhibition of pancreatic insulin and c-peptide secretion may be due to a direct action of IGF-II (Van Schravendijk et al., 1987).

Primary malignant fibrous histiocytoma of the lung is a rare clinical entity (Briselli et al., 1981; Gomez-Roman and Val-Bernal, 1996; Halyard et al., 1996; Juetter et al., 1987; Sato et al., 1996). Malignant fibrous histiocytoma has a low sensitivity to radiation and to chemotherapy, so that surgical resection is the first choice (Halyard et al., 1996). Spindle cells are a common histologic feature of many mesenchymal tumors (fibromas, fibrosarcomas, mesotheliomas, neurofibromas etc.) but do not indicate the functional status of the tumor. Secretory granules are present in some tumors, but their presence also does not correlate with the development of clinical hypoglycemia. Expression of messenger RNA (mRNA) for IGF-II in neoplasms also does not always appear to predict the development of hypoglycemia in patients. IGF-II mRNA without hypoglycemia has been found in Wilms' tumors (Reeve et al., 1985) and pheochromocytomas (Haselbacher et al., 1987), tumors that have been rarely reported to cause hypoglycemia. In these cases, IGF-II may augment tumor growth without causing hypoglycemia. Only a few cases of malignant fibrous histiocytomas are reported with hypoglycemia (Lessel and Erbstosser, 1984). One case-report in 1992 could document an association between an IGF-II-producing histiocytoma (left upper retroperitonel space) and hypoglycemia (Wasada et al., 1992).

In the present case, we documented that tumor-associated hypoglycemia in a patient with a primary malignant fibrous histiocytoma of the lung may be due to IGF-II production. Primary surgical resection normalized hormone levels and glucose metabolism.

References

Baxter R, Daughaday W: Impaired formation of the ternary insulin-like growth factor-binding protein complex in patients with hypoglycemia due to nonislet cell tumors. J Clin Endocrinol Metab 73: 696–702, 1991

Briselli M, Mark E, Dickersin G: Solitary fibrous tumor of the pleura: eight new cases and review of 360 cases in the literature. Cancer 47: 2678–2689, 1981

Chamberlain M, Taggart D: Solitary fibrous tumor associated with hypoglycemia: an example of the Doege-Potter-syndrome. J Thorac Cardiovasc Surg 119: 185–187, 2000

Daughaday W, Trivedi B: Measurement of the derivated of pro-insulin-like growth factor II in serum by radioimmunoassay directed against the E-domain in normal subjects and patients with non-islet cell tumor hypoglycemia. J Clin Endocrinol Metab 75: 110–115, 1992

Dauhaday W, Emanuele M, Brooks M, Barbato A, Kapadia M, Rotwein P: Synthesis and secretion of insulin-like growth factor II by leiomyosarcoma with associated hypoglycemia. N Engl J Med 319: 1434–1440, 1988

Doege K: Fibro-sarcoma of the mediastinum. Ann Surg 92: 955–960, 1930

Eastman R, Kahn CIn: Moore TW, Eastman RC (eds) Philadelphia: BC Decker, Endocrine Diagnostics, 183–200, 1990

Enzinger F, Latties R, Torloni H: Histoligical typing of soft tissue tumors. International Histological Classification of Tumours No. 3. Geneva: World Health Organization 291969

Gomez-Roman J, Val-Bernal J: A case of malignant fibrous histiocytoma of the lung arising as a third primary tumor. Thorac Cardiovasc Surg 44: 321–323, 1996

Halyard M, Camoriano J, Culligan J, Weiland L, Allen M, Pluth J, Pairolero P: Malignant fibrous histiocytoma of the lung. Report of four cases and review of the literature. Cancer 78: 2492–2497, 1996

Haselbacher G, Irminger J, Zapf JWH. Z, Humbel R: Insulin-like growth factor II in human adrenal pheochromocytomas and Wilms' tumor: expression at the mRNA and protein level. Proc Natl Acad Sci USA 84: 1104–1106, 1987

Juetter F, Popper H, Sommersgutter K, Smolle J, Friehs G: Malignant fibrous histiocytoma of the lung: prognosis and therapy of a rare disease. Report of two cases and review of literature. Thorac Cardiovasc Surg 35: 226–231, 1987

Lessel W, Erbstosser E: Malignant fibrous histiocytoma of the lung. Z Erkr Atmungsorgane 163: 70–74, 1984

Marks V, Teale J: Hypoglycemia in the adult. Bailliere's Clinics in Endocrinolgy and Metabolism 7: 705–729, 1993

Potter R: Intrathoracic tumors. Case report. Radiology 14: 60–61, 1930

Reeve A, Eccles M, Wilkins R, Bell G, Willow L: Expression of insulin-like growth factor II transcripts in Wilms' tumor. Nature 317: 258–260, 1985

Sato K, Hagiwara K, Iwaya F, Ogawa T, Hoshino S: A case of malignant lung fibrous histiocytoma. Kyobu Geka 49: 1115–1118, 1996

Teale J, Marks V: Inappropiately elevated plasma insulin-like growth factor II in relation to suppressed insulin-like growth factor I in the diagnosis of non-islet cell tumour hypoglycaemia. Clin Endocrinol 33: 87–98, 1990

Van Schravendijk C, Foriers H, Van den Brande J, Pipeleers D: Evidence of the presence of type I insulin-like growth factor receptors on rat pancreatic A and B cells. Endocrinology 121: 1784–1788, 1987

Vollmar F, Wockel W: Paraneoplastic hypoglycemia due to malignant histiocytoma (Doege-Potter syndrome). Zentralbl Allg Pathol 121: 134–138, 1977

Wasada T, Hizuka N, Yamamoto M, Haruki K, Ikejiri K, Oka Y, Aiba M, Hirata Y: An insulin-like growth factor II-producing histiocytoma associated with hypoglycemia: analysis of the peptide, its gene expression, and glucose transporter isoforms. Metabolism 44: 310–316, 1992

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