PARATHYROID CARCINOMA OF THE MEDIASTINUM

Zhivko V. Peshev, Borislav B. Borisov1, Sylvia N. Genova, Vladimir H. Danev.
Department of General and Clinical Pathology and Forensic Medicine, Medical University of Plovdiv;
1Department of Invasive Cardiology, St George University Hospital, Plovdiv, Bulgaria

ABSTRACT
Parathyroid carcinoma accounts for about 4% of all diseases of the parathyroid glands. It usually presents as a tumor mass in the neck region. Mediastinal parathyroid carcinoma has been reported very rarely.

The present paper reports an ectopic parathyroid carcinoma in the anterior mediastinum in a 54-year male that failed to be recognized antemortem. The markedly elevated serum calcium levels were repeatedly put down to laboratory errors, and the clinical features of primary hyperparathyroidism were misjudged and managed only symptomatically.

The terminal cardiogenic shock was associated with myocardial infarction. Coronary plastic surgery was carried out and a stent was placed.

The postmortem examination found a solid elastic tumor mass (4 cm) firmly encapsulated in the upper half of the anterior mediastinum having trabecular structure, mild nuclear and cellular polymorphism, single irregular mitoses and an area of necrosis. The mass invaded the capsule and the surrounding adipose tissue, there were tumor emboli found in the lymph and blood vessels. Immunohistochemical study showed diffuse expression of low molecular weight cytokeratin, chromogranin A and synaptophysin, and more than 20% of the tumor cells were Ki-67 positive. Glycogen granules were found in their cytoplasm.

There were clearly seen metastatic calcifications in the intramural coronary vessels, the cardiomyocytes, the kidneys and the lungs.

The present case report contributes considerably to the differential diagnosis of hypercalcemia.

Key words: mediastinum, ectopic parathyroid carcinoma, metastatic calcification

INTRODUCTION
Parathyroid carcinomas account for approximately 4% of all disorders of the parathyroid glands.1 Ectopic cases are even more rare: in a series of 17 tumors only two parathyroid carcinomas were located in the mediastinum.2 In most cases this type of neoplasms are accompanied with primary hyperparathyroidism (high levels of parathyroid hormone and serum calcium), and are complicated by hypertension, ischemic heart disease, arrhythmias and heart failure. The low incidence of parathyroid neoplasms makes it difficult to study the mortality rate associated with them.3

CASE PRESENTATION
A man suffered cardiogenic shock as a consequence of clinically undetected hypercalcemia and died shortly after insertion of a biometal stent in the descending branch of the left coronary artery (H.P.S., 54 years old, Disease History 3779/2011).

For a year the patient had been complaining of easy fatigue, ostealgia and myalgia, especially in the shoulder region, constipation, depression and memory impairment. On ambulatory examination the patient was found to have high levels of creatinine, urea and serum calcium, the elevated serum calcium being regarded as laboratory error. Abdominal CAT found concrements in both kidneys. The patient was admitted to the emergency room of the Interventional Cardiology Clinic with pains in the shoulder region and the chest; blood pressure 60/30 mm Hg, leukocytosis - 15.5 G/l, high levels of creatinine, 503 μmol/l, urea 39.5 mmol/l, serum calcium, 6.2 mmol/l and glucose, 8.6 mmol/l.
Figure 1. Parathyroid carcinoma: a - autopsy findings; b - vascular tumor emboli HE(x20); c - microscopic structure HE(x10).

Figure 2. Heart: a - coronary vessel with calcinosis and a stent inserted; b - metastatic calcifications in cardiomyocytes and intramural vessels HE(x20).

Figure 3. Kidney: a - macroscopic view; b - nephrocalcinosi HE(x20).
ECG evidence of heavy ST depressions in II, III, aVF and the entire thoracic series, and ST elevation in aVR, suspicious for stem occlusion or high-grade stenosis. Primary percutaneous transluminal coronary angioplasty of critical stenosis of the left descending branch of coronary artery was carried out. Immediately after this procedure the patient developed asystole and died.

In the postmortem examination we found a tumor mass firmly encapsulated in the upper half of anterior mediastinum with a diameter of 4 cm, with thick, elastic consistency and greyish-yellow area of 1 cm in diameter (Fig. 1a). The histological study found it to be of diverse, mostly solid, trabecular structure, with mild nuclear and cell polymorphism, single irregular mitoses and a necrotic area (Fig. 1b). The tumor mass invaded the capsule and the surrounding adipose tissue and tumor emboli in the lymphatic and blood vessels were seen (Fig 1c). In PAS reaction glycogen granules were found in the cytoplasm. Immunohistochemically, the cells expressed diffuse low molecular weight cytokeratin, chromogranin A and synaptophysin, and Ki-67 in more than 20% of tumor cells.

The heart was enlarged (600 g) at the expense of pronounced concentric left ventricular hypertrophy. In the proximal two thirds the descending branch of the left coronary artery had a normal width, with mild, slightly prominent fibrous atherosclerotic plaque. Distally, 3 cm from the beginning, there was a sharply narrowed area with a metal stent inserted into it (Fig. 2a). The myocardium was light brown, speckled by chaotically arranged whitish thin strips. Microscopic examination revealed pronounced metastatic calcification affecting diffusely single and clusters of cardiomyocytes, walls of the intramural arterial vessels and the presence of hyaline thrombi in the lumen of some vessels (Fig. 2b).

Atherosclerotic changes were poorly presented along the intima of the aorta and the cerebral arteries. Ischemic acute renal failure and marked nephrocalcinosis were found in the kidneys (Figs 3a, 3b). The lungs were edematous, with confluent pneumonia and metastatic calcification in the vascular walls and the interalveolar septa.

DISCUSSION
Because they are very rare, parathyroid carcinomas account for only 0.5% to 1% of the causes of primary hyperparathyroidism.

It is easy to explain the difficulties in diagnosing ectopic cases, as here we have an even rarer combination of ectopy (impaired embryonal development) with neoplastic transformation of the parathyroid gland. The clinical picture is nonspecific: easy fatigue, memory disturbance, loss of appetite, constipation, weight loss, ostealgia, polyuria, all of which are long-standing symptoms which cannot be managed by a symptomatic treatment. The only signs to indicate a tumor of the parathyroid glands are the unusually high serum parathyroid hormone levels (10-52 ng/l) and calcium levels (normal 2.2 - 2.5 mmol/l). Cases without functional activity are few. If there are clinical indications the tumor can be detected by CT but the carcinomas of ectopic parathyroid glands tend to be found only at the postmortem.

Preoperative differentiation of morphological diagnosis is difficult. Mediastinoscopy, the small biopsy materials and express histological study did not provide sufficiently objective assessment of the malignant nature of the tumor. Criteria for malignancy were the presence of necroses, hemorrhage, capsular and peri-neural invasion, tumor emboli in the lymph and blood vessels and finding out distant metastases. Tumor cells contain glycogen while immunohistochemically they show an expression of low molecular weight cytokeratin, chromogranin and synaptophysin. Ki 67, more than 5% should also be considered as a criterion for malignancy.

The increased risk of cardiovascular complications is associated with high serum calcium levels. This leads to metastatic calcifications affecting the myocardium - cardiomyocytes and conduction system. Calcium deposits are present in the intima of the intramural vessels in the myocardium and the coronary vessels. Serum levels of calcium above 3 mmol/l are considered an indication for surgical removal of tumors of the parathyroid glands.

CONCLUSIONS
High level of serum calcium is a sign of an active hyperparathyroidism, and tumors of the parathyroid glands are a frequent cause for it. Absence of any tumor mass in the neck region should suggest that adenoma or carcinoma in an ectopic gland, possibly in the mediastinum should be sought to find.

The more frequent development of cardiovascular complications in primary hyper-parathyroidism involves an increased risk of death. In our case, the immediate cause of death is the massive deposition of calcium in the cardiomyocytes, in the wall of...
intramural blood vessels and the coronary vessels. A timely surgery to remove the tumor is the only efficient therapeutic modality.

REFERENCES

ПАРАЩИТОВИДНАЯ КАРЦИНОМА В МЕДИАСТИНУМЕ
Ж. Пешев, Б. Борисов, С. Генова, В. Данев
РЕЗЮМЕ
Паразитовидная карцинома представляет 4% всех заболеваний паразитовидных желез. Объяснено её как опухолевую формацию в области шеи. Описаны только единичные случаи с локализацией в медиастинале.
Представлена нераспознанная прижизненно эктопическая паразитовидная карцинома в переднем отделе медиастинала у мужчины 54 лет. Экстремально повышенные уровни сыроваточного кальция несколько раз считались лабораторной ошибкой, а клинические признаки первичного гиперпаратиреоидизма недооценились и лечение симптоматическое.
Финальный кардиогенный шок связан с инфарктом миокарда. Проведена коронаропластика и поставлен стент.

При обдукции в верхней половине переднего медиастинала обнаруживается хорошо капсулированная плотная эластическая опухоль (4 см) с трабекулярным строением, легким ядерным и клеточным полиморфизмом, с единичными неправильными митозами и с некротическим участком.
Устанавливаются инвазии в капсулу и в окружающей жировой ткани, опухолевые эмболии в лимфатических и кровеносных сосудах. Иммуногистохимическое исследование показывает диффузную экспрессию низкомолекулярного цитокератина, хромогранина A и синаптофиллини, а Ki-67 позитивируется более чем в 20% всех опухолевых клеток. В их цитоплазме обнаруживаются гликогеновые гранулы. В интрамуральных коронарных сосудах и в кардиомиоцитах, в почках и легких устанавливается выраженный метастатическое кальцинирование.
Настоящее наблюдение представляет существенный вклад в дифференциально-диагностическое выяснение гиперкальциемии.