MEDIASTINAL MALIGNANT NON-CHROMAFFIN PARAGANGLIOMAS: DIAGNOSIS AND CHOICE OF TREATMENT

Summary. Objective: thoracic mediastinal non-chromaffin paragangliomas are very rare tumors. They can arise from chemoreceptor at multiple sites throughout the body. The diagnosis was provided by the histological examination of the surgical specimen. Patients and methods: the paper presents the personal experience of the authors in the examination and treatment of 26 patients with mediastinal paraganglioma, 25 of them were malignant. Conclusion: it was the first experience to put into practice the intra-arterial selective combined chemotherapy with significant clinical effect. Total resection after intra-arterial chemotherapy is the best approach to the treatment of malignant paragangliomas.

INTRODUCTION

Paraganglioma (PG) is a tumor, originates from neural crest of sympathetic and parasympathetic paraganglia. According to Classification of World Health Organization, PG are included in group of paragangliomas and glomal tumors. The term “non-chromaffin paraganglioma” is applied mostly in respect to the tumors, which arose from non-chromaffin paraganglia. These tumors are called also granular cell tumor, alveolar tumor, carcinoid, and chemodectoma. The malignant parasympathetic PG (malignant chemodectoma) is characterized by slow growth and later metastasis. The closeness of PG cells to nerve cells and fibers argues not only on their genetic, but also functional affinity. It is supposed that non-chromaffin PG secret polypeptide hormones, which are not catecholamines.

Mostly they are detected in the area of carotid body, jugular fossa, orbit, in spinal canal, retroperitoneal space. Along with it there are reports on their more rare localization: thyroid gland, urinary bladder, prostate gland, iliac region, lung, heart, mediastinum [2–4, 9, 22–24]. The capacity of multifocal growth is considered to be the peculiarity of these tumors [7, 8, 13, 21]. These tumors are frequently idiopathic, but in researches are described family cases, which constitute 7-9% of all PG, when they are inherited by autosomal-dominant type [19, 21]. Thereupon the clinical and radiologic investigation of patient’s relatives should be recommended [19].

Intrathoracic PG, which localize mostly in mediastinum, are rare tumors, which distinguish themselves by complexity of presurgical diagnostics and choice of appropriate method of therapy at presence of extensive infiltrating growth. The size and localization of PG of mediastinum are variable, they often acquire big sizes, and the prior localization of these tumors is anterior mediastinum, where paraaortal parasympathetic ganglia become the source of their development [1]. However, there are reports on localization of PG in posterior mediastinum. Probably, they originate from paravertebral chain of sympathetic ganglia [2, 9, 17].

The microscopic structure of PG of any localization is of the same type. Depending on grouping of cells, amount of stroma and vessels, the alveolar (alveolar-trabecular), trabecular, angiomatous and solid variants of PG are separated. These
variants are often combined in the same tumor, but usually the one out of them is considered to be prevalent. Malignant variant of tumor, by diffused opinion, is rarely found and is characterized by apparent infiltrating growth[17, 21, 25]. The metastases of malignant PG arise relatively late, firstly in regional lymph nodes, than the hematogenic metastasis takes place. The observations of patients with malignant PG with presence of multiple organ metastases, including lungs, liver, bones, brain, orbit, have been described [15, 24, 25].

According to the B. Baysaland co-authors, the criterion of malignancy of PG is based on clinical progression of disease more, than on histopathologic feature [7]. PG without cellular atypia can diffuse in hematogenic way in regional lymph nodes or further organs, though metastases are rarely to be found. The group of Americano-authors [16] has researched the angiogenesis at pheochromocytomas and PG and has concluded that the apparent vascular network of tumor correlates with its capacity for invasive growth and that angiogenesis of tumor can be used for the estimation of malignant behavior of PG. At presence in mediastinum of non-chromaffin non-secretory PG, which is characterized by local growth, the clinical presentation of tumor is regularly minimal and the disease is being uncovered occasionally by computer tomography (CT) or magnetic resonance tomography (MRT), which were carried out concerning other diseases [12, 18, 21]. The choice of treatment tactics at non-chromaffin PG of mediastinum is conditioned by particular objective data. The radical surgical removal remains the standard of treatment cause of danger of progressing growth of tumor and its low sensitivity to the chemotherapy (CT) and radiotherapy (RT) [26].

Basing on the analysis of own long-term clinical experience and data of researches, we have set the task to estimate the results of different treatment approaches and to define the optimal method of treatment of patients with malignant PG of mediastinum as well as to separate the main prognostic factors of studied category of patients.

PATIENTSANDMETHODS

In department of the thoracic oncology of National Institute of Cancer from 1968 till 2012 have been observed 26 patients with PG of intrathoracic localization, 25 out of them are with neoplasm in mediastinum (24 – in anterior, 1 – in posterior).

Approximately equal distribution of patients by sex has been observed – 14 women and 12 men. The age of patients fluctuated from 14 to 74. All patients have been clinically examined with wide application of instrumental methods, including CT, endoscopic, functional and cytomorphologic investigations. The diagnostic surgeries (parasternal mediastinotomy, thoracotomy, biopsy of enlarged peripheral lymph nodes) have been conducted in 13 patients. In 10 of them has been verified malignant PG. Transthoracic needle biopsy of tumor for cytological research has been carried out in 13 patients.

The surgical intervention was performed in 17 patients, in 12 out of them the surgery was a component stage of complex or combined treatment, in 3 – independent treatment, in 2 – has ended with trial thoracotomy. The combined treatment, which included the presurgical RT and surgery, has been performed in 6 patients. Complex treatment, performed in 6 patients, has included neo-adjuvant CT, in 3 – in combination with RT. In 5 out of these patients has been applied the strategy of regional intra-arterial injection of antitumor chemodrugs. The patients with the presence of single metastases have received the palliative treatment: 4 – RT, 5 – independent polychemotherapy (PCT).

The distant RT has been carried out with use of devices “ROKUS-AM” or “Teratron-Elit 80” with emitter Co60; the single focal dose – 2,0 Gr, total focal dose – up to 40 Gr.

RESULTS AND DISCUSSION

Themajorityof patients – 17 (65,4%) – have entered the clinic with diffused tumor process, in 8 of them (30,8%) were detected metastases (in 4 – in supraclavicular lymph nodes, 4 – in lungs, pleura, 2 – in bones). However, the particular research data argue that metastases at PG develop rarely – in approximately 5-10% of cases [8, 9].

In our case patients with PG of mediastinum by clinical stages have been divided into the following way: I (T1N0M0) stage — 1, II (T2N0M0) — 5, III (T3N0M0) — 11, IV — presence of remote metastases (M1) — 8 and (T4N2M0) — 1.
Clinical presentation of non-chromaffin PG of mediastinum depends on degree of diffusion of tumor, its localizations and capacity for infiltrating growth. At malignant variants of PG, which are localized in anterior mediastinum, the symptoms of compressive syndrome prevail, including syndrome of compression of superior vena cava that was marked in the majority of observed by us patients. PG of mediastinum may be locally invasive, grow into aorta and its branches, pulmonary artery, pericardium, heart that conditions the clinical symptomatic.

The most typical subjective symptoms, which make our patients to appeal for medical aid, are pains in chest, sternal pain in heart area (in 23 patients). M. Brownet and co-authors have described the case of detection of PG of anterior mediastinum at coronary arteriography, being conducted on the occasion of atypical pain in the heart area and dyspnea [7]. Blood supply of tumor was carried out by branches of coronary artery.

The basic method of detection of tumor remains the routine radiological investigation, which allows to determine the presence of pathological tissue in mediastinum, mostly in its anterosuperior section. Sizes, configuration and localization of shadow-forming in many respects are determined by the type of tumor growth—encapsulated (non-malignant) or infiltrating (malignant). For non-malignant PG is typical the presence of unilaterally located paramediastinal shadow of circular or oblong shape, of medium intensity, with smooth accurate outlines. In lateral projection PG localize near the arch of aorta, occupying the anterior or anteromedial parts of mediastinum, rarely — posterior. Themalignant tumours usually are located behind the sternum, medium, stipulating for radiologically determined dilatation of median shadow in upper part, outlines of shadow are accurate, here and there uneven.

CT or MRI of mediastinum allows to determine the true location of tumor, involving the adjacent structures and anatomic formations in pathological process. The specific investigation for PG is scintigraphy with $^{123}$- or $^{131}$-metaiodobenzylguanidine (MIBG-scintigraphy). MIBG accumulates significantly more in malignant PG in contrast to non-malignant, providing by this the diagnostic criterion of differentiating of these tumors [18, 26]. MIBG-scintigraphin combination with CT provides anatomic and functional information with good sensitivity (80–90%) and specificity (95–100%) [18].

Presurgical diagnosis is verified by cytological and histological tests of the material, obtained by needle biopsy of tumor or by mediastinoscopy. According to R.Rana and co-authors, cytological peculiarities are quite clear at diagnostics of PG[20]. However, at cytological test of material of needle biopsy of tumors of 13 our patients in none of the cases was determined the right morphological diagnosis. Only in 1 patient at immunohistochemical test of tumor’s punctate has been diagnosed malignant PG.

The character of PG growth predetermines the opportunity of its radical removal. According to the opinion of majority of authors, the treatment of PG of mediastinum shall be surgical, excluding malignant variants with presence of single metastases. At infiltrating growth of tumor and its association with great vessels, heart, trachea, the radical removal becomes impossible or is coupled with significant technical obstacles and possible hard intraoperative complications. C. Andrade and co-authors have described the case of PG, which localized in aorticopulmonary window, which surgical removal was complicated by massive bleeding, which was stopped only by tamponade of pleural plane[5]. K.S. Williams and co-authors have brought the example of PG of medium mediastinum, which was diffusing intrapericardially, tightly knitted with aorta at the bottom of right coronary artery[27]. The elimination of tumor has been complicated by sharp massive hemorrhage in volume up to 4 L of blood.

Out of 26 of our patients the different methods of treatment were undertaken by 24. The surgeries have been performed in 17 patients, out of them radical surgeries in 13, palliative — in 2 and trial thoracotomies — in 2. Out of number of radical surgeries in 7 patients together with removal of tumors has been performed resection of adjacent anatomic structures (lung, pericardium, left brachiocephalic vein). Only in 3 patients the treatment has been limited with independent radical surgery. Out of these patients 1 patient have lived 34 months and 1 is under the observation after the surgery during 26,9 months. The combined treatment (pre-operative RT and surgery) has been conducted in 6 patients and complex treatment (neo-adjuvant CT or CT in combination with RT) — in 6 patients. There were no complications before and after the surgery.
According to the opinion of M. Brown, the lifespan of patients does not depend on even efficacy of removal (full or partial) of PG and constitutes from 3 to 13 years [7]. In observations of the author, after partial removal of PG of mediastinum the patients have lived for 14 years without progression of disease. In observation of L. Mancini, F. Roncaroli patient with malignant PG of mediastinum was alive during 27 years after surgical removal of tumor [17]. Together with it, there are reports on development of metastases after full removal of tumor after a long period of time [20].

The attitude to RT at inoperable PG is controversial – from the estimation of method as effective, which allows authors [2] to recommend inclusion of the irradiation in combined treatment at malignant PG, to negative attitude to this method of treatment [25]. We seem to be possible to find the explanation of such controversial statements in diversity of histological types of PG. Basing on our observations, we may remark the moderate sensitivity of PG to RT, in majority of patients, who have received RT as pre-operative or independent treatment, has been detected the progression of tumor growth. Only 1 patient after radical removal of PG with pre-operative RT has been observed without progression of tumor during the 5 years 10 months; 5 patients have died from prolongation of disease in terms from 5.5 to 48 months, the average lifespan of their lives after treatment constituted 32.7 months. After trial thoracotomy with pre-operative RT the patient have lived more than 3 years, one more patient after palliative removal of tumor with pre- an after-operative irradiation have lived for 21 months.

There are single reportson application of CT in treatment of patients with malignant PG [2, 15, 25]. A. Argiris and authors, applying metastatic form of PG of CT with cyclophosphamide 700 mg/m² on 4-th day, doxorubicin 40 mg/m² on 1-st day and dacarbazine 375 mg/m² on 1-st day, have remarked the apparent clinical improvement, but, at the same time, did not detect significant changes of tumor on computer tomography; patient is under the observation without progression of disease during 24 months [6]. Temporary improvement of laboratory data and 20% downsizing of metastases in liver in result of application of cyclophosphamide 700 mg/m² on 4-th day, vincristine 1 mg/m² on 3-rd day and dacarbazine 375 mg/m² on 1-st day in patients with malignant metastasizing PG has been registered by S. Kimura and co-authors [15]. By experience of H. Huang and co-authors, who applied this regimen of CT in patients with malignant PG, has been obtained convincing palliative effect with median survival 3.3 years [14]. According to our observations, positive direct effect and better results of recurrence-free survival of patients with PG have been obtained at conducted treatment, which included CT. The significant decrease of expression of both clinical symptoms of compressive syndrome (including syndrome of compression of superior vena cava) and radiologically registered sizes of tumor in mediastinum has been achieved in the result of carried out regional intra-arterial PCT. The malignant PG in the majority of patients was found to be sensitive to CT, which was carried out by several blocks, included cisplatin (50 mg/m² on 1-st day), cyclophosphamide (700 mg/m² on the 4-th day), vincristine (1 mg/m² on 3-rd day) and dacarbazine (375 mg/m² on 1-st day); in certain patients, to the CT scheme was added doxorubicin (40 mg/m² on 1-st day) or etoposide (100 mg/m² on 1; 2; 3-rd day). The lifespan of patients after carried out complex treatment with use of mentioned chemodrugs has constituted from 23 months to 8 years 7 months, 2 patients are under the observation during 83 and 104.6 months. The average lifespan in this group of patients has constituted 58.3 months.

We bring one of our observations. Patient M., 31 years old, have entered the department of tumors of organs of thoracic cavity on 03.12.2007 with diagnosis “tumor of mediastinum. Thymoma?”. To the moment of admission the patient has presented the problems of dry cough, dyspnea during physical activity, pain in right half of thorax, increase of body temperature up to 37.5 °C in evenings, skin itch. For the verification of diagnosis the transthoracic needle biopsy of tumor of mediastinum has been conducted twice, however, no qualifying information, but data, which indicated the malignance of tumor, have not been obtained. 06.12.2007, have been conducted the diagnostic thoracotomy from the right, biopsy of tumor, catheterization of both inner thoracic arteries. On the basis of data of pathohistological (Fig.1) and immunohistochemical tests as well as results of spiral CT has been established clinical diagnosis “malignant PG of mediastinum”. Metastases of PG in lymph nodes in the root of right lung, paratracheal lymph nodes.

Fig.1 Malignant poorly-differentiated tumor – PG. Staining by hematoxylin and eosin; × 200
From 18.12 to 21.12.2007, patient has obtained cycle of intra-arterial PCT (cisplatin 50 mg/m² on 1-st day, etoposide 100 mg/m² on 1; 2; 3-rd days, vincristine 1 mg/m² on 3-rd day). From January till May, 2008, with interval in 3 weeks have been conducted 4 cycles of systemic PCT by the same scheme, inasmuch catheters in both inner thoracic arteries were thrombosed, despite the prophylactic heparin therapy. The course of PCT patient has been satisfactory. 26.05.2008, in patient was performed the removal of tumor of mediastinum with resection of upper part of left lung, resection of pericardium, total mediastinal lymphodissection. According to data of pathohistological investigation of removed tumor – malignant PG with apparent therapeutic pathomorphosis, the volume of vitalized tumor tissue constituted 23.7% (Fig. 2,3). 10 days after surgery patient has been discharged from hospital in satisfactory condition.

3 months later, at control examination progression of tumor has been detected – the increase of supraclavicular lymph nodes from the right sized up to 1.5–2 cm, solitary metastasis in S₁ of liver up to 5 cm in diameter. The wide lymphodissection of supraclavicular part into the right has been performed. In removed lymph nodes has been verified the presence of metastases of malignant PG. The cycle of PCT by scheme has been carried out: ifosfamide (3.0 mg/m² on 1; 2; 3-rd days) + doxorubicin (40 mg/m² on 1-st day). Later on patient has obtained 5 more cycles of PCT by the same scheme in regional oncological dispensary by place of residence. 25.06.2009, patient was operated on the occasion of metastasis in liver. The resection of S₁, liver with metastasis of malignant PG has been performed. The conclusion of histological investigation: in liver, lymph nodes the excrescence of poorly-differentiated tumor – malignant PG.

Fig. 2. Therapeutic pathomorphosis in the form of large-focal necrosis of tissue of tumor. The staining by hematoxylin and eosin; ×200

Fig. 3. Therapeutic pathomorphosis in the form of large-focal necrosis of tumor tissue. The staining by hematoxylin and eosin; ×400

At present time the condition of patient is satisfactory, there are no data on progression of disease.

Own accumulated experience allows us to conclude the following:

1. Non-chromaffin PG of mediastinum develops with the same frequency both in men and women, independently from age of patients.
2. Out of 26 patients being observed, in 25 of them histologically were confirmed malignant PG that allows us do not agree with presented in researches statements about high rarity of malignant variants of PG of mediastinum.
3. The specified preoperational diagnosis of PG of mediastinum is difficult and is possible only with help of histological (immunohistochemical) investigation of bioptic or operational tumor material.
4. PG of mediastinum are mostly located in anterior part, upper floor, in area of arch of aorta and great venous trunks of mediastinum.
5. Formalignant PG of mediastinum the typical features are infiltrating growth, rooting into adjacent anatomic structures, high density of vascularization, fast growth of tumor and capacity for metastasis.
6. The majority of histological variants of malignant PG of mediastinum are moderately sensitive to ionizing irradiation. RT makes palliative therapeutic impact.
7. Antitumor CT, which includes cisplatin, vincristine, dacarbazine, and cyclophosphamide, makes apparent therapeutic impact upon the majority of variants of malignant PG. Regional intra-arterial CT is the method of choice as preoperational treatment of malignant PG of mediastinum.

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