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V. Zakharychev [1], B. Borysyuk [2], P. Gordiichuk [1, *]

[1] Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine
[2] State Non-Commercial Enterprise «National Cancer Institute», Kyiv, Ukraine

* Correspondence: Email: zakharych2014@gmail.com

OBSERVATION OF SUCCESSFUL TREATMENT OF MALIGNANT METASTATIC PARAGANGLIOMA OF THE MEDIASTINAL AORTOPULMONARY WINDOW

A unique observation of the successful complex treatment of a rare and clinically complex metastatic mediastinal paraganglioma is presented. It has been shown that neoadjuvant intra-arterial regional chemotherapy with the subsequent surgical removal of the tumor can be an effective method of choosing treatment for malignant metastatic mediastinal paraganglioma.

Keywords: mediastinum, metastases of malignant non-chromaffin paraganglioma, surgical, complex treatment, intra-arterial regional chemotherapy.

The World Health Organization defines a paraganglioma (PGL) as a tumor that synthesizes, stores, and secretes catecholamines outside the adrenal glands and can occur anywhere in the body [1]. Mediastinal PGL originates from the chromaffin cells of extra-adrenal sympathetic ganglia, which are located around large vessels [1—3]. These rare tumors account for only 0.3% of mediastinal tumors and 1%—2% of all PGLs [4, 5]. The choice of the treatment tactics for a non-chromaffin PGL of the mediastinum is determined by specific objective data. The radical removal remains the standard of treatment due to the threat of progressive tumor growth and, according to some authors [4, 6—9], low sensitivity to chemotherapy or radiation therapy.

The aim of the work was to present a unique case of successful treatment of a patient with malignant metastatic PGL of the aortopulmonary mediastinum.

Case report. The patient, a 31-year-old woman, was admitted to the Department of Tumors of the Chest Cavity of the National Cancer Institute, Kyiv, Ukraine, with a diagnosis of tumor of the anterior mediastinum (thymoma?). At the time of admission, she complained of a dry cough, shortness of breath during physical exertion, pain in the left half of the chest, subfebrile body temperature in the evenings, and itchy skin. A neoplasm in the upper part of the anterior mediastinum, which is adjacent to the arch of the aorta and the left pulmonary artery, was determined on the radiograph and CT scan of the chest cavity (Fig. 1, *a, b*).

To verify the diagnosis, a transthoracic puncture biopsy of the mediastinal tumor was performed

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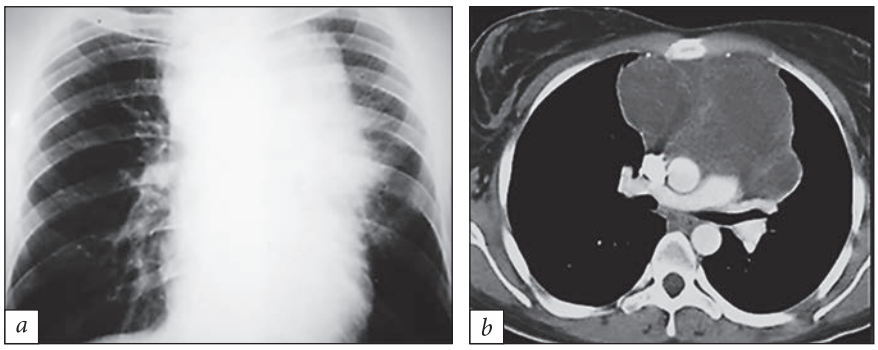

Fig. 1. X-ray image of the chest cavity: bilateral expansion of the middle shadow in the upper part (*a*). Chest CT: anterior superior mediastinal tumor adjacent to the aortic arch and left pulmonary artery, into which the tumor grows (*b*)

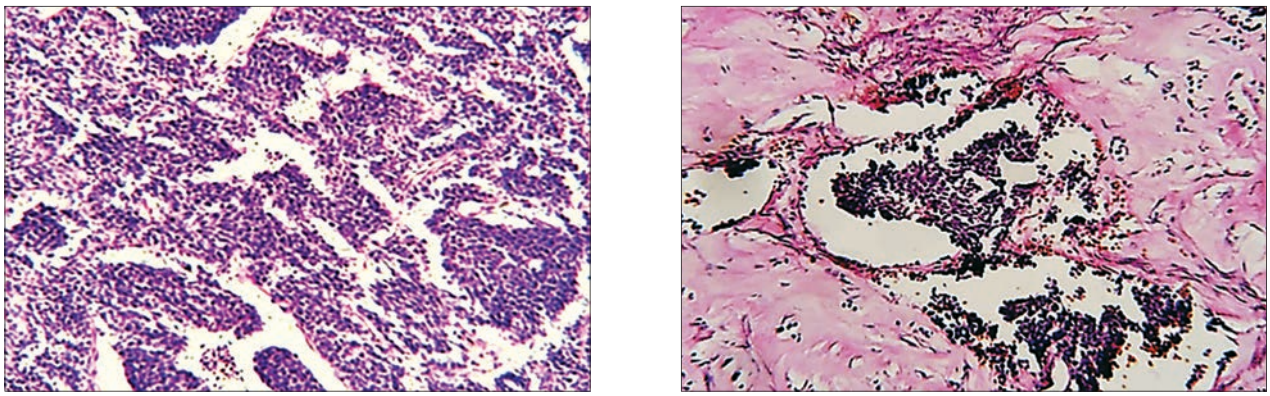

Fig. 2. Malignant poorly differentiated tumor paraganglioma. Staining with hematoxylin and eosin; ×200
Fig. 3. Therapeutic pathomorphosis in the form of large focal necrosis of tumor tissue. Staining with hematoxylin and eosin; ×400

twice; however, apart from the data on the presence of elements of a malignant tumor, no clarifying information was obtained. Diagnostic mediastinotomy, tumor biopsy, and catheterization of both internal thoracic arteries were performed. Based on the data of pathohistological examination (Fig. 2), as well as spiral CT data, a clinical diagnosis was established to be malignant PGL of the anterior mediastinum, tumor metastases in the lymph nodes of the root of the right lung, and paratracheal lymph nodes.

The patient received a cycle of intra-arterial chemotherapy (CTX) according to the scheme of cisplatin + lastet + vincristine. For 5 months, 4 more cycles of systemic CTX were performed with three-week intervals by a similar scheme, because the catheters in both internal thoracic arteries were thrombosed despite prophylactic heparin administration. The patient passed the CTX course satisfactorily. After 3 weeks, a radical removal of the mediastinal tumor was performed with resection of the upper lobe of the left lung and the left pulmonary artery, resection of the pericardium, and total mediastinal lymphadenectomy (lymphodissection). The pathohistological and immunohistochemical studies revealed a pronounced medical pathomorphosis with viable tumor tissue amounting to 23.7% (Fig. 3). In 10 days after the surgery, the patient was discharged home in satisfactory condition.

After 3 months, a follow-up examination revealed the progression of the disease: an increase in the cervical-supraclavicular lymph nodes on the right to 1.5—2 cm and a solitary metastasis in the liver in S5 up to 5 cm in diameter (Fig. 4).

A wide lymphodissection of the cervical-supraclavicular region on the right was performed. The presence of metastases of malignant PGL was confirmed in distant lymph nodes. A cycle of CTX according to the scheme of ifosfamide + doxorubicin was carried out. Later, the patient received 5 CTX cycles by this scheme. After that, the patient underwent an operation for the liver metastasis. S5 resection of the liver with metastasis of malignant PGL was performed. The conclusion of the histological examination: in the liver, in the lymph nodes, the

growing low-differentiated tumor is malignant PGL. The postoperative course was smooth, and the patient was discharged in satisfactory condition. During the control 7-year examination of the patient, no sign of disease progression was found. The patient's expected prognosis is favorable without further relapses.

As far as we know, there has never been such a case of proven effective treatment of malignant metastatic PGL. This report may increase confidence in surgical operations for metastatic mediastinal PGLs.

PGL without cellular atypia can metastasize to the regional lymph nodes or distant organs by hematogenous spread, although metastases are rare. The nature of the PGL growth determines the possibility of its radical removal. The treatment of PGL of the mediastinum should be surgical, except for malignant variants with the presence of distant metastases [7—9]. Some reports in the literature indicate that mediastinal PGLs are usually well-differentiated and slow-growing benign tumors [1]. Metastases are rarely observed (about 5—10% of the observations [2, 10]. However, of our 29 patients with intrathoracic localization of PGL, of whom 28 were with localization in the mediastinum and 1 in the pericardial cavity, in 9 (31%) cases, distant metastases were detected (in the cervical and supraclavicular lymph nodes, liver, lungs, pleura, or bones). Overall, 15—35% of PGL have been shown to undergo malignant transformation, with the recurrence occurring in approximately 20% of cases [11].

Out of 15 radical operations, 7 patients underwent resection of adjacent anatomical structures (lungs, pericardium, left brachiocephalic vein) along with tumor removal.

The attitudes toward radiotherapy (RT) in inoperable PGL are contradictory — from evaluating the method as effective, which allowed the authors [10] to recommend including irradiation in the combined treatment of malignant PGL, or as negative [1, 12]. We can find an explanation for such contradictory judgments in the variety of the histological types of PGL. Based on our observations, we can note a moderate sensitivity of PGL to RT. Progression of tumor growth was detected in the majority of patients who underwent RT as a preoperative or independent treatment. Only one patient, after the radical removal of mediastinal PGL with preoperative RT was observed without tumor progression for more than 6 years; 5 patients died from the prolongation of the disease for a period of 5.5 to 48 months. The average life expectancy of patients in this group after treatment was 32.7 months. After a trial thoracotomy with preoperative RT, one patient lived for more than 3 years, and another patient lived for 21 months after the palliative removal of the tumor with pre- and postoperative radiation of the mediastinum.

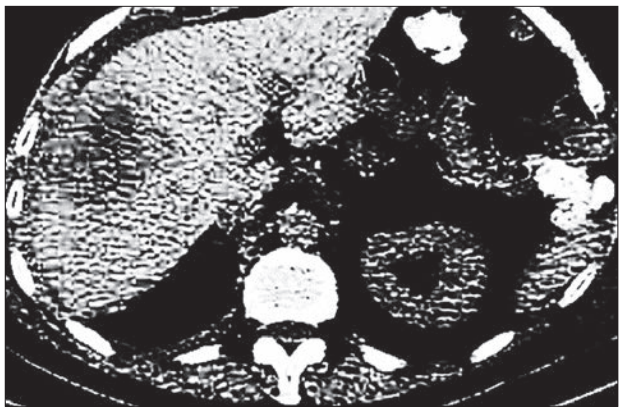

Fig. 4. CT scan of abdominal organs. Solitary metastasis in S5 liver

Intra-arterial chemotherapy is based on the following provisions: preoperative therapy used with surgery should not negatively affect the outcome of the operation and should contribute to the reduction and size of the local tumor mass and thus to increase resectability. The therapy should affect distant subclinical metastases and minimize side effects so that patients can tolerate specialized treatment before and after surgery. The use of intra-arterial chemotherapy depends on the type of tumor to be treated, the source of blood supply, the effective dose of the chemotherapy drug, concentration, and exposure periods of drug administration, as well as systemic and regional toxicity and the method of delivery.

Malignant PGL in most patients was found to be sensitive to combination CTX performed in several blocks, which included cisplatin, vincristine, ifosfamide, and dacarbazine. In some patients, doxorubicin was added. The life expectancy of the patients after complex treatment with the use of these anticancer drugs was from 43 months to 8 years and 7 months, and 2 patients were observed for 93 and 104.6 months. The average life expectancy in this group of patients was 68.3 months.

Antitumor CTX, which includes cisplatin, vincristine, ifosfamide, and doxorubicin, has had a

pronounced therapeutic effect on most variants of malignant PGL, including metastatic forms. The neoadjuvant intra-arterial regional CTX followed by surgical removal of the tumor may be a method of choice for the complex treatment of malignant mediastinal PGL.

Our observations allow us to disagree with the statements available in the literature about the utmost rarity of malignant variants of mediastinal PGL.

This case highlights the successful surgical treatment of a rare and clinically challenging mediastinal PGL without cardiopulmonary bypass. The report emphasizes the importance of rapid diagnosis and comprehensive treatment of metastatic mediastinal PGL.

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В. Захаричев [1], Б. Борисюк [2], П. Гордійчук [1]

[1] Національний університет охорони здоров'я України ім. П. Л. Шупика

[2] Державне некомерційне підприємство «Національний інститут раку», Київ, Україна

СПОСТЕРЕЖЕННЯ УСПІШНОГО ЛІКУВАННЯ ЗЛОЯКІСНОЇ МЕТАСТАТИЧНОЇ ПАРАГАНГЛІОМИ МЕДІАСТИНАЛЬНОГО АОРТОПУЛЬМОНАЛЬНОГО ВІКНА

Представлено унікальне спостереження за успішним комплексним лікуванням рідкісної та клінічно складної метастатичної медіастинальної параганглюми. Показано, що неоад'ювантна внутрішньоартеріальна регіональна хіміотерапія з подальшим хірургічним видаленням пухлини може бути ефективним методом вибору лікування злоякісної метастатичної медіастинальної параганглюми.

Ключові слова: середостіння, метастази злоякісної параганглюми, хірургічне, комплексне лікування, внутрішньоартерійна регіональна хіміотерапія.