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Malignant paraganglioma of the urinary bladder. Description of clinical cases

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Paraganglioma is hormonally active tumor originating from chromaffin tissue of sympathoadrenal system that secrete large amounts of catecholamines. Paraganglioma of the urinary bladder is a rare neoplasm, constituting approximately 0.06 % of all tumors of this localization. It is believed that this disease arises from embryonic remnants of chromaffin cells in the sympathetic plexus of the detrusor. Up to 10 % of these tumors have malignant origin. Diagnosis and tactics of treatment of patients with malignant paragangliomas of the bladder presents certain difficulties. The article describes 2 clinical observations of patients with this bladder pathology.

Key words: *extraadrenal pheochromocytomas, paraganglioma of the urinary bladder, diagnosis, scintigraphy with MIBG, transurethral resection of the bladder, radical cystectomy*

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Paraganglioma is a hormonally active tumor originating from chromaffin tissue of the sympathoadrenal system and secreting large amounts of catecholamines. Usually, these tumors develop in the adrenal medulla, and they are called pheochromocytomas. About 10 % of all pheochromocytomas develop outside of the adrenal gland. Extra-adrenal pheochromocytomas (paragangliomas) are usually paraaortic and emerge from the ganglions of the sympathetic nervous system. Paragangliomas of the bladder are rare: They comprise about 0.06 % of all tumors of the bladder, and about 10 % of all paragangliomas [1–4]. It is believed that this disease arises from embryonic remains of chromaffin cells in the sympathetic plexus of the detrusor [5].

In 1953, I.J. Zimmerman et al. described a clinical observation of a paraganglioma of the bladder. Since then, about 250 cases of pheochromocytomas of the bladder were described in literature. In about 10 % of these tumors, metastases in the pelvic lymph nodes were diagnosed, therefore, about 25 cases were malignant paragangliomas of the bladder [3, 6–9]. The symptom of malignancy of these tumors is distant and regional metastases. Currently, there are no reliable histological tests to distinguish between malignant and benign paragangliomas.

The disease onsets in the 2nd or 3rd decade of life. This pathology is 3 times more common in women than in men [10]. The largest existing study (L. Cheng et al.) included only 16 cases of the disease [11]. According to the authors, in 37 % of patients at the time of diagnosis propagation of the pathological process to paravesical tissue or involvement of the neighboring organs are observed.

Although pheochromocytomas of the bladder are sporadic, there»re familial forms of the disease [12]. In case of the latter, probability of malignancy is about 50 %, which is much higher than 10 % for sporadic paragangliomas of the bladder [13].

The majority (83 %) of pheochromocytomas are hormonally active and are accompanied by a specific clinical picture caused by excessive production of catecholamines. Frequently, patients note hypertensive crises, accompanied by headaches, excessive sweating, tachycardia, and hot flushes. Constant and paroxysmal forms of arterial hypertension are the most common symptoms of paragangliomas of the bladder: they are observed in 60–70 % of patients. About 60 % of patients complain of painless macrohematuria [14, 15]. Researchers note a certain specific symptom of pheochromocytoma of the bladder known as micturition attack which is observed in about 50 % of patients with this pathology [16].

During the diagnosis, a tumor located, primarily, near the tip of the bladder or the trigone is observed [17].

In the N.N. Blokhin Russian Oncological Research Center, 2 cases of malignant paragangliomas of the bladder were diagnosed. These clinical observations we now present to the readers.

Clinical case 1

Female patient B., *14 years. The patient was hospitalized at the Surgery Department # 2 of the Research Institute of Pediatric Oncology and Hematology of the N.N. Blokhin Russian Oncological Research Center from 28.03.2011 to 05.05.2011.*

At admission: complaints of increased blood pressure, headaches. From medical history: In October of 2010, the patient sought medical help at the local out-patient facility for recurrent increased blood pressure. Complete physical examination revealed a tumor of the bladder, cystoscopy with tumor biopsy were performed. Histological report: paraganglioma of the bladder. The child was referred to the Research Institute of Pediatric Oncology and Hematology for a decision

on further treatment. After an examination at the out-patient facility of the Research Institute of Pediatric Oncology and Hematology and revision of the histological samples, the paraganglioma of the bladder diagnosis was confirmed.

***Results of clinical diagnostic examination**. Computed tomography of the thoracic and abdominal organs, retroperitoneal space, and lesser pelvis (21.02.2011): no lesions or infiltration changes in the lungs, thoracic lymph nodes of normal size. In the cavity of the lesser pelvis between the posterior bladder wall and the rectum, a mass with amorphic irregular margins of dimensions 9.0 × 4.8 × 4.8 cm is observed (Fig. 1). The uterus is pushed back, ovaries are not visualized. An expansion of the collecting system of the left kidney to 3.4 cm and the left ureter is observed (Fig. 2). In the distal area, the ureter is pressed by the tumor. Collecting system of the right kidney without changes. Renal scintigraphy (13.03.2011): total renal function moderately decreased. Cystoscopy (16.03.2011): plica interureterica, opening of the left ureter, posterior wall of the bladder, mucosa are raised, with bullous edema and ulceration covered by fibrin. The opening of the left ureter is not defined. Radioisotope examination of the bone tissue (30.03.2011): no lesions in the bones. Ultrasound of the abdominal organs, retroperitoneal space (31.03.2011): the right kidney of normal size, pyelocaliceal system not expanded, the left kidney is enlarged due to expansion of the pyelocaliceal system to dimensions 10.1 × 5.1 × 5.0 cm, the left ureter is enlarged to 1.2 cm. The bladder with uniform contents, a thickening on the posterior wall of dimensions 4.0 × 2.5 cm is observed. Scan with radiopharmaceutical MIBG (I 131-labeled MIBG (iodine-131-m-iodobenzylguanidine)) (31.03.2011): specific activity of chromaffin nature in the lesser pelvis. Considering the clinical and instrumental data, histological nature of the tumor, a decision to perform surgical treatment at the 1st stage was made.*

On 05.04.2011 laparotomy, bladder resection, reimplantaion of both ureters, two-sided pelvic lymph node dissection were performed. The postoperative period was smooth.

Considering the results of histological examination, type of the tumor, the patient received 4 courses of adjuvant polychemotherapy per the following regimen: vincristine 1.4 mg/m^2 intravenously (IV) bolus at day 1, cyclophosphane 750 mg/m^2 IV infusion+ mesna 100 % from the cyclophosphane dose at day 1, dacarbazine 600 mg/m^2 IV infusion at days 1 and 2. During dynamic observation at the Research Institute of Pediatric Oncology and Hematology, in February of 2016 complete physical examination didn't show any recurrence or progression of the disease.

Clinical case 2

***Male patient K.**, 29 years. The patient was hospitalized at the Urology Department of the N.N. Blokhin Russian Oncological Research Center from 20.07.2014 to 20.08.2014. From medical history: In 2001, at 17 the patient noted blood in urine, pain in the lower part of the abdomen, episodic increased arterial blood pressure. At the local facility, cystoscopy was performed revealing tumor of the bladder. Magnetic resonance tomography of the abdominal organs and lesser pelvis (2001): extra-organ tumor in the lesser pelvis of dimensions 4.4 × 3.2 × 3.0 cm with pathological process affecting the posterior wall of the bladder, infiltration of paravesical and pararectal tissue. In 2001 at the local facility the patient underwent transurethral resection of the bladder. Histological report (histological samples were reviewed at the N.N. Blokhin Russian Oncological Research Center): parts of tumor have paraganglioma structure. The patient sought medical assistance at the N.N. Blokhin Russian Oncological Research Center.*

Considering histological type of the tumor, the patient was offered surgical treatment which he refused, choosing drug therapy at the local facility. In 2002, the patient received 10 courses of polychemotherapy per the VAC scheme (vincristine, doxorubicin, cyclophosphane) in combination with beam therapy of the bladder (total dose 50 Gy) with positive effect in the form of decreased tumor size. Until 2013, the patient was monitored at the local facility without symptoms of disease progression.

In 2013, episodes of painless macrohematuria resumed, the patient noted dysuric disorders. At the local facility, com-

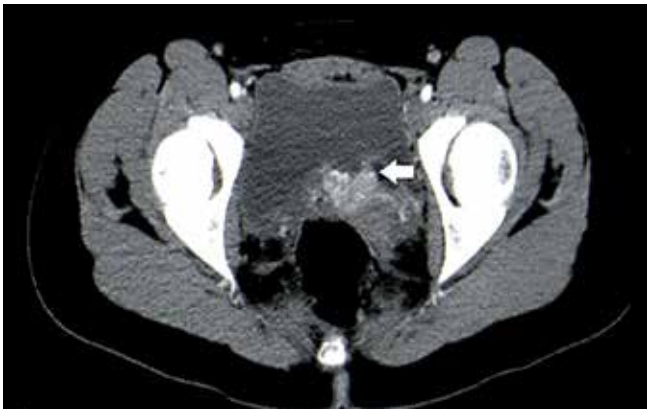

Fig. 1. *Female patient B.: computed tomography of the lesser pelvis with intravenous amplification, axial plane. Arrow shows a tumor of the bladder*

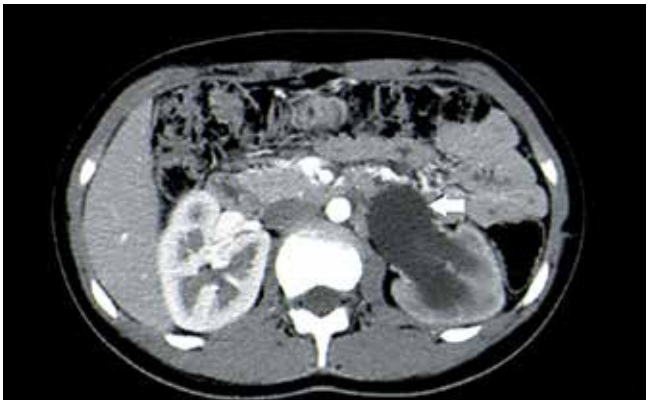

Fig. 2. *Female patient B.: computed tomography of the lesser pelvis with intravenous amplification, axial plane. Arrow shows expanded pelvis of the left kidney*

plete physical examination revealed recurrence of the disease, left ureterohydronephrosis. In 2013, at the local facility the patient underwent transurethral resection of the bladder. A nephrostomy tube was installed on the left, later it was removed. The patient was again referred to the N.N. Blokhin Russian Oncological Research Center for a decision on further treatment.

After a revision of histological samples at the N.N. Blokhin Russian Oncological Research Center and an immunohistochemical examination of the postoperative material of 2001, 2013, the following conclusion was made: histological structure and cell immunophenotype correspond to paraganglioma (2001), recurrence of the disease in 2013. The patient was offered surgical treatment which he once again refused. The patient received a consultation from a chemotherapist: polychemotherapy regimen cisplatin 50 mg/m^2 + doxorubicin 50 mg/m^2 with subsequent effect evaluation was recommended. In 2014, the patient received 6 courses of polychemotherapy per the recommended scheme.

At the follow-up examination in May of 2014, negative dynamics were observed: signs of left ureterohydronephrosis, increased size of the tumor in the lesser pelvis, metastatic lesion in the iliac lymph nodes. X-ray computed tomography of the lesser pelvis with intravenous contrast (16.05.2014): walls of the bladder thickened to 1.2 cm, behind the bladder (in the posterior wall? adipose tissue?) a mass with amorphic rugged margins of irregular shape is observed with intense and heterogeneous contrast accumulation with subsequent fast removal, of dimensions 3.8 × 1.4 cm, adjacent to the seminal vesicles and prostate (Fig. 3). Behind the right external iliac vessels, a lymph node of size 2.6 × 1.7 cm with distinct regular margins and intense and heterogeneous contrast accumulation with subsequent fast removal is observed. Two similar lymph nodes of size up to 0.8 cm are observed behind the left iliac vessels (Fig. 4). The rectum without pathology. A nephrostomy tube was installed paracentetically on the left. Capacity of conservative treatment was considered exhausted, the patient was offered surgical intervention which he accepted.

On 06.08.2014 the patient underwent surgery consisting of radical cystoprostatectomy, Studer»s procedure.

During dynamic observation at the N.N. Blokhin Russian Oncological Research Center and the follow-up examination in July of 2016 no recurrence or progression of the disease were observed.

Morphological examination of these 2 tumors of the bladder showed their similar histological structure: The tumors consisted of small and large alveolar structures comprised of large cells with wide light or grainy eosinophilic cytoplasm (Fig. 5), located in scanty matrix with vessels of the sinusoid type without necrotic lesions. Number of mitoses varied between 3–4 and 6–7 in 10 fields of view at 400x magnification. Solitary tumor emboli were observed in the lymph sinuses. In the lymph node samples taken for examination, tumor metastases with similar structure were detected (Fig. 6). Immunohistochemistry revealed expression of chromogranin A (Fig. 7), NSE marker (Fig. 8), and the S-100 protein in the tumor cells. Proliferation index of the tumor cells varied between 1 and 3 %. Based on morphological structure and immunohistochemistry, considering metastases in the regional lymph nodes, malignant paraganglioma was diagnosed.

Discussion

Diagnosis of paraganglioma of the bladder is associated with certain difficulties. The levels of catecholamines and their metabolites in serum and urine are usually within normal limits. Most commonly, tumors are located in the submucosal layer, and about 80 % of these neoplasms can be detected during cystoscopy [18]. These tumors are often covered by normal mucosa (in contrast to typical exophytic component in transitional cell carcinoma of the bladder) [19, 20]. Biopsy during cystoscopy for histological confirmation of the paraganglioma of the bladder diagnosis is controversial, because it can cause hypertensive crisis with possible fatal complications. There»re reports of this kind of complications during this diagnostic manipulation in literature. In patients presented in our clinical observation, transurethral resection of the bladder and «cold» biopsy weren»t accompanied by complications of this type.

Both patients underwent computed tomography. Sensitivity of this type of examination for paraganglioma of the bladder is 82 %, although use of magnetic resonance tomography in different modes demonstrated higher sensitivity for diagnosis of neoplasms in this location. Thus, T1-weighed images allow to evaluate condition of the regional lymph nodes and expansion to the paravesical tissue, while T2-weighted images can reveal infiltration of the bladder wall which allows to gather information on tumor advancement [20]. Scan with MIBG radiopharmaceutical is the most effective method for diagnosis of extra-adrenal pheochromocytomas, its sensitivity reaches 100 %. [21]. This method was used in 1 patient and showed a tumor in the lesser pelvis (see description in the text).

Differential diagnosis of paraganglioma of the bladder and rhabdomyosarcoma of the bladder, hemangioma, neurofibroma, transitional cell carcinoma, and even bladder stones should be performed. The latter should be considered because several cases of calcified tumors were described in literature [22, 23].

Summary literature data show that between 5 and 10 % of paragangliomas are malignant. However, currently there aren»t any pathohistological symptoms allowing to differentiate between malignant and benign paragangliomas [11]. Malignancy of paraganglioma of the bladder is defined primarily by its clinical symptoms. Metastases are a definite sign of malignant cancer. The most common area of regional metastasis for these tumors is the pelvic lymph nodes. In our observations, metastases in the pelvic lymph nodes were observed in both patients.

Surgical treatment of local paragangliomas of the bladder includes complete tumor removal with bladder wall

resection. Additionally, dissection of the pelvic lymph nodes is recommended for diagnosis. If metastases in the pelvic lymph nodes at diagnosis are confirmed, S. Das et al. recommend radical cystectomy with pelvic lymph node dissection [1]. Despite some studies on transurethral resection of the bladder in treatment of paragangliomas of this localization, currently it»s considered insufficient. Y. Takezawa et al. don»t recommend transurethral resection of the bladder as a radical method of paraganglioma treatment because of possible intense emission of catecholamines and subsequent increase in arterial blood pressure during surgery, as well as because of a possibility of non-radical intervention caused by insufficient visualization of the tumor due to its location (usually, in the submucosal layer of the bladder) [24].

In our observation, in 1 patient complete physical examination didn»t present verifiable data on metastases in the pelvic lymph nodes, so a decision was made to perform surgery consisting of bladder resection with two-sided pelvic lymph node dissection. In the 2nd patient, metastases in the regional lymph nodes were confirmed before the surgery, so he underwent radical cystectomy.

There's data on sensitivity of paragangliomas of the bladder to chemotherapy and beam therapy in literature [25]. In 1988, S.D. Averbuch et al. described CVD (cisplatin, vinblastin, dacarbazine) chemotherapy courses in patients with paraganglioma of the bladder, noting a decrease in tumor volume by 56 % [26]. S. Yoshida et al. published a clinical observation of a case of paraganglioma of the bladder noting a positive effect of beam therapy rep-

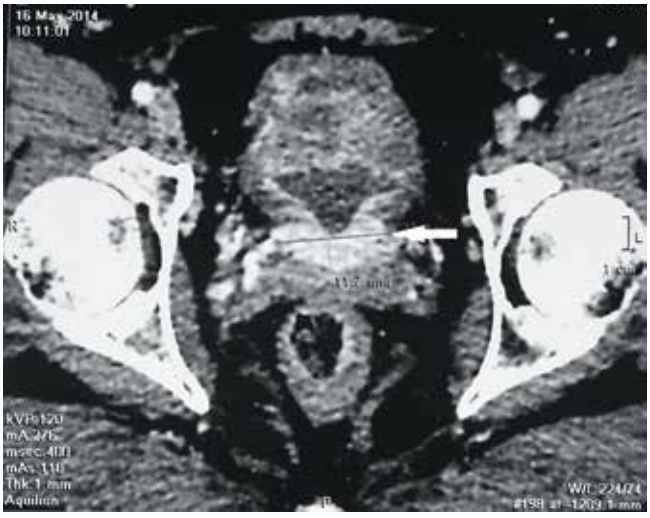

Fig. 3. *Male patient K.: X-ray computed tomography of the lesser pelvis with intravenous amplification, axial plane. Arrow shows a tumor of the bladder actively accumulating contrast agent*

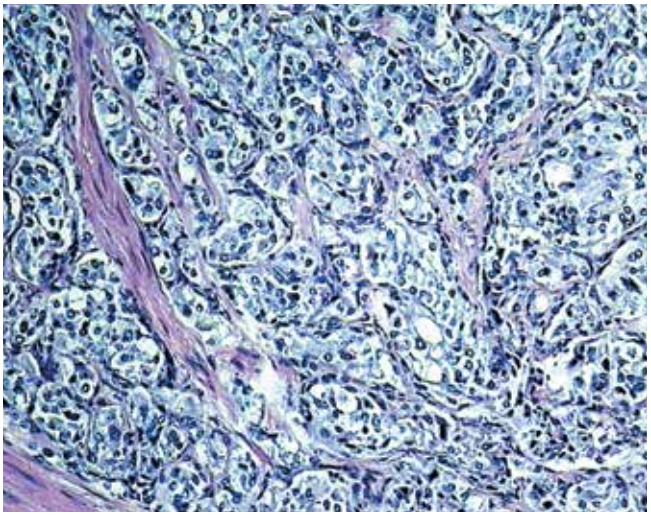

Fig. 5. *Morphological structure of paraganglioma (infiltrative growth). Alveolar structures of the tumor consisting of cells with wide grainy cytoplasm in the muscle layer of the bladder wall. Hematoxylin and eosin stain. 200*

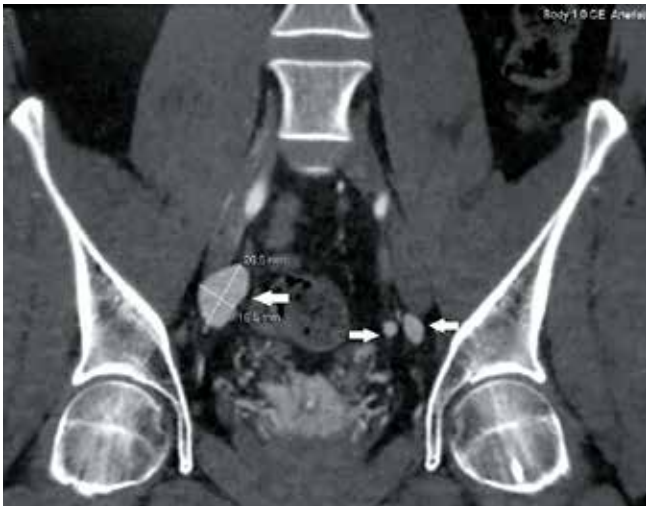

Fig. 4. *Male patient K.: X-ray computed tomography of the lesser pelvis with intravenous amplification, frontal plane. Arrows show enlarged iliac lymph nodes actively accumulating contrast agent*

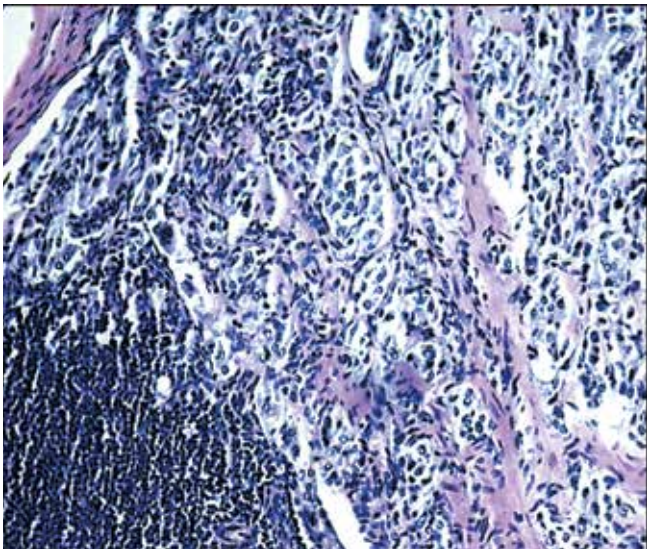

Fig. 6. *Metastasis of paraganglioma in the lymph node. 100*

resented by decreased tumor size and blood catecholamine level [27].

In our observation, the 2nd patient also underwent external beam therapy which resulted in decreased tumor size. The patient stayed in remission for a long period of time (11 years), but the disease still progressed.

Beam therapy can be considered an option for patients with inoperable forms of paraganglioma of the bladder and as accompanying therapy for CVD polychemotherapy.

Postoperative tactics of patient monitoring are still being argued. The necessity of dynamic observation of patients with the tumor due to its unpredictable behavior should be noted because there're literature data on local recurrences and metastases 20 and more years after the surgery [1, 8, 25].

During dynamic observation, blood catecholamine level should be monitored and scans with MIBG radiopharmaceutical should be performed [18, 28]. Computed tomography and magnetic resonance imaging can also be considered.

Because of histological data of the 1st patient showing metastases in the regional lymph nodes, we considered adjuvant chemotherapy necessary in this case. Both patients remain under dynamic observation at the N.N. Blokhin Russian Oncological Research Center due to risk of late recurrences of malignant paraganglioma of the bladder.

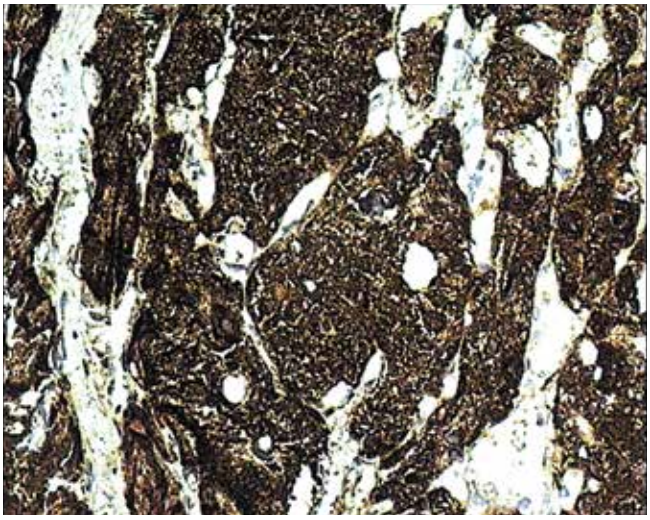

Fig. 7. *Pronounced expression of chromogranin A in the paraganglioma cancer cells. × 200*

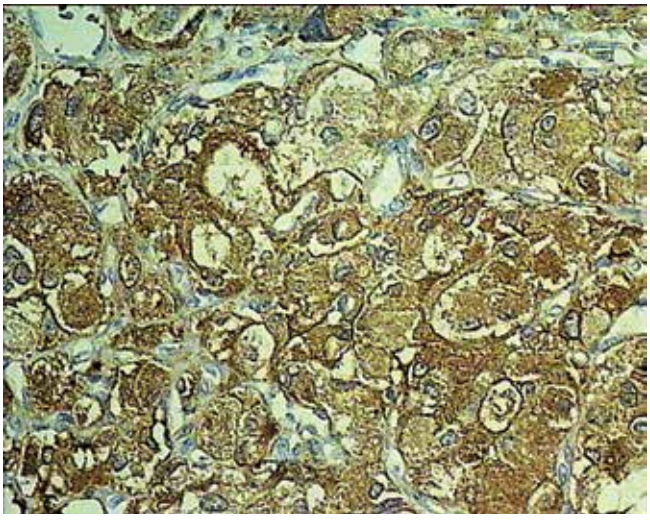

Fig. 8. *Expression of NSE in the paraganglioma cancer cells. × 200*

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