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CASE REPORT

Patient with inoperable pheochromocytoma

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ABSTRACT

Malignant pheochromocytoma is a tumour with a very low incidence that occurs sporadically or in the presence of multiple endocrine neoplasia. We present the case of a woman with a sporadic occurrence of pheochromocytoma diagnosed in the phase of multiple dissemination in the abdominal cavity and overexpressing adrenaline, noradrenaline, and dopamine. Local transarterial chemoembolization and systemic treatment with lanreotide resulted in a very good response, a decrease in the production of catecholamines for 12 months and a partial decrease for another 8 months, with stabilization of disease determined by imaging.

Systemic treatment with tegafur resulted in disease stabilization lasting 50 months, after which the drug was discontinued because of adverse effects. Maintenance therapy with lanreotide continues, and no disease progression has been observed for 4 months.

The treatment algorithm for such patients is multidisciplinary and must always take into account the current scope of the disease, intercurrence, and the general condition of the patient.

Key Words Pheochromocytoma, chemoembolization, lanreotide

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INTRODUCTION

Pheochromocytoma belongs to the neuroendocrine tumour group, and its incidence is 2–6 new cases per 1 million population. In recent years, improvements in diagnosis and, in particular, searches for the cause of secondary hypertension have been revealing more tumours (pheochromocytoma causing only about 0.05%–0.1% of cases) at earlier stages.

The incidence of pheochromocytoma is generally sporadic, but 24% of cases are related to hereditary syndromes (type 2 multiple endocrine neoplasia, von Hippel–Lindau disease, and type 1 neurofibromatosis).

In patients with pheochromocytoma, *RET, VHL, NF1* germline mutations in *SDHB, SDHC, SDHD, SDHAF2, KIF1B,* and *PHD2* have been detected, which holds some significance mainly for diagnosis. In sporadic pheochromocytoma, mutations in transmembrane protein 127 (*TMEM127*)—which probably controls the PI3K/Akt/Ras signalling pathway—have been identified and could be associated with the response to treatment with inhibitors of mTOR (the mammalian target of rapamycin) [1]. In familial syndromes, the occurrence of malignant (metastatic) pheochromocytoma is less than 5%. Pheochromocytomas arise from chromaffin cells and secrete catecholamines. In most cases, they are found in the adrenal gland medulla. The malignant forms constitute about 17% of all cases; malignancy is more frequent in sporadic occurrences [2].

Medical prognosis in pheochromocytoma is related to the number of metastases and their locations. If metastases are found only in bones, the prognosis is much more favourable. If dissemination to the liver, lungs, or other organs is also present, then the chance of cure is minimal, and more than 50% of patients die within 5 years of diagnosis [3].

Treatment of disseminated disease has two targets: paraneoplastic hormone production, and the mass of malignant cells. If surgical resection is not possible, the option of local ablative therapies or intra-arterial treatment (for example, with chemoembolization) can be considered [4,5]. If the resulting effect is insufficient, then systemic chemotherapy can be administered. Some experience with cyclophosphamide, vincristine, and dacarbazine has been reported [6]. A partial response, with acceptable toxicity, can be expected in about 55% of cases; however, there is very little experience in this area. Better response to systemic treatment with inhibitors of mTOR and heat shock proteins is expected. Experience with cytostatic therapy is small; administering a curative dose of radionuclides [7] appears to be more suitable for tumours that trap radionuclides.

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CASE DESCRIPTION

A 76-year-old woman had first been taken ill at the age of 59. In 1996, she underwent surgery for a symptomatic tumour of the mesentery (abdominal pain, weight loss). After a complete surgical resection, malignant pheochromocytoma was diagnosed. Subsequently, only ultrasonography monitoring of abdomen was indicated, plus clinical checks and determination of 5-hydroxyindoleacetic acid in urine.

The patient experienced no problems and had no medical findings until 2009, when both lobes of the liver were found to be extensively affected by inoperable multiple metastases. A liver biopsy again pointed to a neuroendocrine tumour: a malignant pheochromocytoma with histology identical to that in 1996.

The patient experienced nausea, weight loss, and worsening hypertension, but no flushing, tachycardia, or paroxysms. She was not breathless. The clinical findings established hepatomegaly without ascites.

Computed tomography (CT) showed an inoperable tumour, with multiple liver metastases in both lobes (maximum size: 25 mm). Ejection fraction by echocardiography was 63%. The patient was treated with beta-blockers and angiotensin converting-enzyme inhibitors for hypertension. Her main problem was fatigue.

The patient's chromogranin level was normal; adrenaline, noradrenaline, and dopamine were elevated to 3 times normal (Table I). An octreotide scan was positive, with a finding of multiple liver metastases; diagnostic scintigraphy with metaiodobenzylguanidine–^{131}I was negative.

In addition to her basic disease, the patient was treated for hypertension (beta-blockers, sartans, diuretics) and type 2 diabetes mellitus (diet and metformin), and for cerebrovascular disease in the form of atherosclerosis, with neurologic manifestations of mixed pyramidal and extrapyramidal rigidity (statins and antiplatelet treatment). Clinical findings were appropriate to her age and overall performance status of 2, which was a contraindication chemotherapy.

TABLE I Change in catecholamine levels with treatment in a pheochromocytoma patient

Treatment timing	Adrenalin (pmol/L)[a]	Noradrenalin (pmol/L)[a]	Dopamine (pmol/L)[a]
Before	3,160.8	10,582.8	6,312.6
After TACE			
First	562.3	4,843.1	1,586.3
Second	5,065.9	14,889.1	457.0
Third	5,415.3	11544.3	1364.3
With tegafur			
Start	5,415.3	11,544.3	1364.3
After 1 year	540.4	2,973.1	692.0

[a] Normal values: adrenaline, 79–459 pmol/L; noradrenaline, 887–2,490 pmol/L; dopamine (3,4-dihydroxyphenethylamine), 131–560 pmol/L.

TACE = transarterial chemoembolization.

Treatment started with transarterial chemoembolization (TACE) using drug-eluting beads impregnated with doxorubicin (Biocompatibles: DC Bead, London, U.K.), which was first performed in June 2009 with good results: catecholamine levels declined, and as determined by CT imaging, her disease stabilized.

Simultaneously, treatment with lanreotide 90 mg every 28 days was started. The effect of the first administration lasted 9 months, after which progression of catecholamine levels and paroxysmal supraventricular tachycardia with spontaneous transition to sinus rhythm occurred. The CT findings showed that the patient was progression-free.

A second round of TACE again stabilized her disease for 6 months, and lanreotide treatment continued.

Further progression (only in the expression of catecholamines) occurred in April 2010, February 2011, and September 2011. Each time, the same treatment was administered, with stabilized disease and maintenance of a good quality of life for the patient being the result (Figure 1). After progression in July 2012, TACE was performed for a third time, but the effect was insufficient, and it failed to improve the patient's clinical condition or to lead to a decline in the level of catecholamines.

After a first reduced dose of cyclophosphamide was administered, acute severe hemorrhagic cystitis resulted (grade 3 by the *Common Terminology Criteria for Adverse Events*). Another systemic anticancer treatment—tegafur 400 mg on days 1–56, followed by a 2-week rest interval—was therefore selected.

Treatment with tegafur was not initially toxic and did not affect the patient's quality of life. The level of catecholamines declined, gradually reaching normal values by July 2013, when treatment had to be discontinued because of adverse effects of tegafur (development of chronic conjunctivitis).

The patient's disease stabilized, and catecholamines did not rise. The CT imaging findings also stabilized. It was not necessary to adjust the patient's antihypertensive medications. Today, the patient continues with only maintenance lanreotide treatment. Her disease is stabilized, she has a reasonable quality of life, and her overall condition has not deteriorated.

DISCUSSION

Overall, only 17% of pheochromocytomas are malignant, and median survival in metastatic pheochromocytoma is reported to be 3.8 years [6] in patients who respond well to chemotherapy. In patients who do not respond, median survival is just 1.8 years. A worse prognosis is associated *SDHB* gene mutation [2] (which was not diagnosed in our patient).

The best-established chemotherapy regimen is a combination of cyclophosphamide, vincristine, and dacarbazine (Averbuch protocol: cyclophosphamide 750 mg/m^2 body surface area on day 1, vincristine 1.4 mg/m^2 on day 1, and dacarbazine 600 mg/m^2 on days 1 and 2 every 21 days). The results of that regimen after 22 years of follow-up in 18 patients demonstrated a complete response rate of 11%, a partial response rate of 44%, a biochemical response rate of 72%, and median survival of 3.3 years [8].

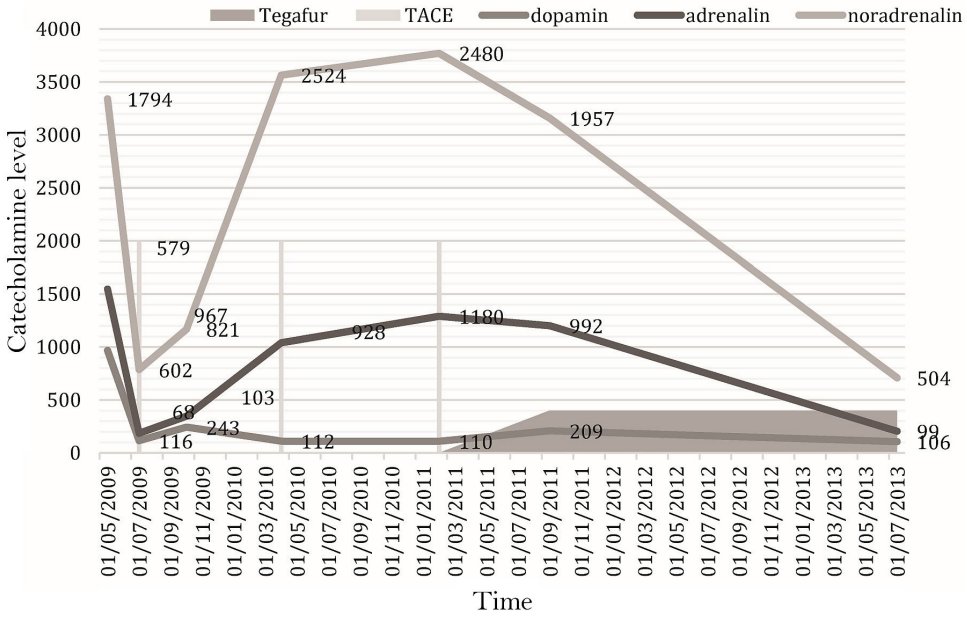

FIGURE 1 Response to three rounds of transarterial chemoembolization (TACE) and tegafur in a pheochromocytoma patient.

Another possibility is a combination including doxorubicin 40 mg/m^2 on day 1, cyclophosphamide 750 mg/m^2 on day 1, vincristine 1.4 mg/m^2 on day 1, and dacarbazine 250 mg/m^2 on days 1–5 every 3–4 weeks, which was administered in a 50-year-old patient, effecting a complete long-term recovery.

The foregoing regimens were not suitable for use in our patient because of their adverse effect profiles. Newer drugs that have been successfully used include everolimus in 4 patients in the RAD001 study [9], with a beneficial effect in pheochromocytoma associated with von Hippel–Lindau syndrome: 2 patients experienced a partial response, and 1 experienced a complete response [10]. In tumours trapping metaiodobenzylguanidine–^{131}I, the probability of response would be high after administration of therapeutic doses. In a study that included 25 patients [11], disease stabilization was achieved in 72% of patients after 6 months, with median survival duration being 18 months. In the patients who died, the mean interval between disease progression and death was 4.6 months (range: 0–12 months). Another potential pheochromocytoma treatment targets heat shock protein 90 [12]; good results in breast cancer have been observed, and the agent is now in clinical trials. A positive effect is considered a high probability.

Tegafur is a fluoropyrimidine that has been proved to work in colorectal cancer. Some experiences in head-and-neck cancer and breast cancer have also been reported. Despite the few, although positive, experiences [13] with derivatives of fluoropyrimidines, we selected tegafur treatment in our patient because of its adverse effect profile. Little experience with antitumour response and decline in hormonal markers has been reported after administration of somatostatin derivatives, but in our patient, those agents were effective.

Somatostatin acts on both endocrine and non-endocrine tissues and is a key regulator of the release of various hormones and growth factors. Its effects have been well proven *in vitro* [14]. Although some initial small-scale studies have indicated a reduction in tumour catecholamine production [15] or symptomatic improvement, those responses have not been confirmed by other groups [16]. However, in our patient, the contribution of treatment with somatostatin analogues in her overall response was clear and led primarily to a reduction in hormone secretion.

Chemoembolization is a highly suitable treatment for hypervascular liver tumours, especially hepatocellular carcinoma. Experience shows that this method provides a good response in liver damaged by neuroendocrine tumours, including pheochromocytoma, despite its rarity [17]. In our patient, the best response was obtained with the first application (Figure 1); in other applications it was able only to stabilize the disease.

SUMMARY

Treatment of our patient with localized TACE and systemic lanreotide resulted a very good response; a decline in catecholamine production for 12 months, with a partial decline for another 8 months, and disease stabilization by CT imaging.

The effect of systemic treatment with tegafur consisted of disease stabilization for 50 months, after which the drug was discontinued because of adverse effects. Maintenance therapy with lanreotide continues, and no disease progression has occurred for 4 months.

The treatment algorithm for pheochromocytoma patients is multidisciplinary, and clinicians must always take into account the current scope of the disease, intercurrence, and the general condition of the patient.

Considering its minimal adverse effects, TACE can be an effective treatment even in a patient with a performance status of 2.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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