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[^{131}I]I-MIBG-negative metastases of a recurrent sporadic paraganglioma in a female with achondroplasia

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We herein report the first case report of a female with achondroplasia in whom ^{131}I-metaiodobenzylguanidine ([^{131}I]I-MIBG) failed to detect any accumulation, while ^{18}F-dihydroxyphenylalanine ([^{18}F]F-DOPA) positron emission tomography (PET) confirmed metastatic recurrent paraganglioma.

A 44-year-old female with achondroplasia was admitted for postoperative follow-up after resection of a metastatic recurrent retroperitoneal tumour, diagnosed as a paraganglioma after histopathological examination.

In 2008, she underwent the first resection of the retroperitoneal tumour, which was diagnosed after histopathological examination as a pheochromocytoma/paraganglioma (PPGL) (immunohistochemical analysis: chromogranin A+, synaptophysin+, proliferation index Ki-67–).

The first time she was admitted to the Department of Endocrinology in April 2009 for postoperative follow-up, with well-controlled hypertension, without any symptoms of sympathetic hyperactivity, with no signs of tumour recurrence in CT of the abdomen, urine metanephrines levels were normal.

In 2010 during an annual check-up, abdominal CT reported a left para-aortic lymph node (9 mm), but urine metanephrines were still normal. In 2011, the same lymph node was 12 mm in diameter, and a 24-hour urine test showed slightly elevated urine normetanephrine excretion, with normal serum chromogranin A level. Still, the patient had no symptoms of recurrent PPGL. A routine genetic test employing conventional sequencing for predisposing mutation in the *RET* gene was negative.

Subsequently, the patient was lost to follow-up for a few years until she reappeared at our institution in December 2018. Again, the biochemical investigations revealed significantly elevated urine concentrations of normetanephrine. Abdominal computed tomography (CT) visualized a polycyclic tumour (30 × 52 × 47 mm) in the retroperitoneal area. After pharmacological preparation with alpha-blockers, the patient underwent resection of the tumour in May 2019, complicated by severe hypovolaemic shock. Due to perforation of the large bowel and peritonitis, a retroperitoneal abscess occurred. Following 2 additional relaparotomies, a terminal ileostomy was created.

Histopathological examination confirmed the diagnosis of PPGL recurrence with the following characteristics on immunohistochemical analysis: chromogranin A: +, synaptophysin: +, Ki-67: + ca. 2–3% cell nucleus, p53: + less than 1% of cell nucleus.

In October 2019 thorax and abdomen CT visualized lymph nodes in the inferior mediastinum, to the left from the aorta (16 × 10 mm), and in other nodes in the retroperitoneal area (8 mm). In January 2020 the patient was admitted to our department with symptoms of tumour biochemical activity, namely tachycardia (110 hb/min) and poorly controlled hypertension (mean blood pressure — 150/100 mm Hg). Urine normetanephrine excretion and serum chromogranin A were elevated, and CT imaging was comparable with the earlier CT. The patient, due to her history, localization, and small dimension of lesions, was disqualified from surgery.

A [^{131}I]I-MIBG scan did not demonstrate any significant radioisotope uptake. Subsequently, PPGL-dedicated positron emission tomography combined with computed tomography with the use of [^{18}F]F-DOPA

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confirmed multiple metastatic lesions in the retroperitoneal area, in the mediastinum, and in bones (Fig. 1). Moreover, somatostatin receptor scintigraphy (SRS) showed no somatostatin receptor expression in the metastatic lesions.

In addition to the previous *RET* testing, we performed targeted next-generation sequencing (NGS) for analysis of a gene panel contributing to PPGL (covering 12 genes: *FH, KIF1B, MEN1, NF1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL*). No predisposing pathogenic germline variants were reported.

Considering the tumour's somatic origin, characterized by slow progression and low Ki-67+ index, radionuclide treatment was discarded and a watchful waiting approach was recommended, including symptomatic treatment with 2 mg of doxazosin. This approach was well-tolerated and led to a good clinical effect.

We report a relatively rare case of MIBG-negative sporadic metastatic and recurrent PPGL in a female with achondroplasia. There are a few other reports describing MIBG-negative pheochromocytoma/PPGL patients [1–3]. As observed by other authors, as in our patient, a negative MIBG scintigram usually indicates a metastatic tumour.

There is some evidence that [18]F]F-DOPA PET-CT is more sensitive than MIBG scintigraphy in PPGL visualization. Rufini et al. showed that [18]F]F-DOPA PET or PET/CT detected recurrent paragangliomas with a sensitivity of 100%, whereas 75% sensitivity was achieved for the [123]I-MIBG scan [4] whereas 38% were detected with [123]I-MIBG ($p = 0.04$). An explanation is the better targeting of chromaffin cells with [18]F]F-DOPA than with radio-iodinated MIBG because of the different uptake mechanism.

In the study by Fiebrich et al., [18]F]F-DOPA PET improved staging by detecting 36 unknown lesions, and it changed the treatment decision in 14 patients. This suggests that routine implementation of [18]F]F-DOPA PET in patients with catecholamine excess is likely to influence patient management [5].

Our case supports the hypothesis that epigenetic changes might cause MIBG negativity in some patients. Further epigenetic and proteomic studies would be beneficial in MIBG-negative PPGL patients, to find novel prognostic factors of metastatic and recurrent outcome.

Conflicts of interest
The authors have no conflicts of interest to disclose.

Consent for publication
Written consent for publication was obtained from the patient.

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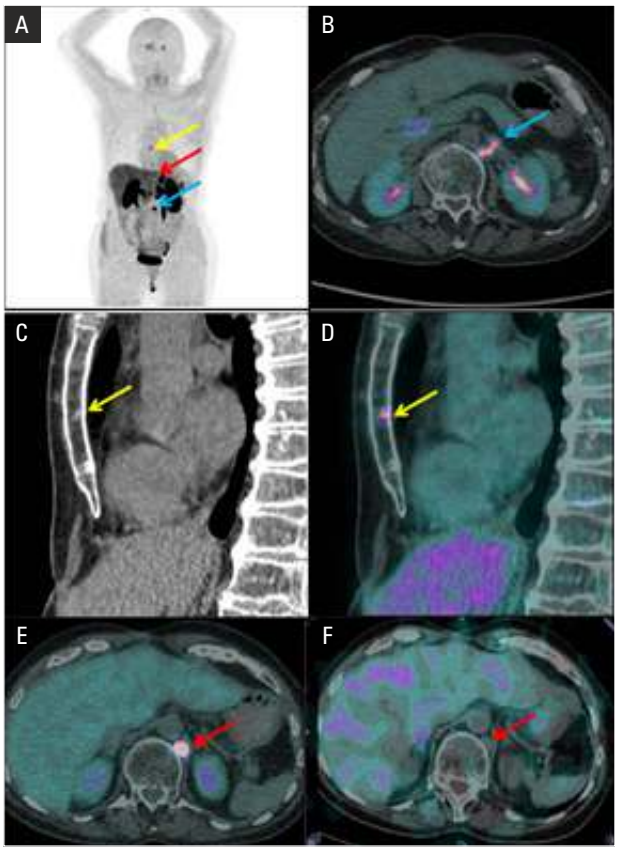

Figure 1. A–E. *[18]F]F-DOPA accumulation in multiple lesions of pheochromocytoma/paraganglioma (PPGL) recurrence: in positron emission tomography (PET) projection (***A***, 3 arrows) and PET/computed tomography (CT) fusion images (***B***, ***D***, ***E***); **B.** Recurrence in the retroperitoneal space (blue arrow); **D.** Small bone metastasis in the sternum (yellow arrow), visible also in the CT alone (***C***, yellow arrow); **E.** Metastatic phrenic lymph node (red arrow); **F.** Single-photon emission computed tomography (SPECT)/CT fusion image showing no [131]I-metaiodobenzylguanidine ([131]I]I-MIBG) accumulation in the same phrenic lymph node (red arrow)*

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