CASE REPORT

¹⁸F-DOPA PET/CT unravels malignant paraganglioma mimicking temporomandibular joint disorder

A Terzić^{*1}, M Becker², M Wissmeyer³ and P Scolozzi¹

¹Service of Maxillo-Facial and Oral Surgery, Department of Surgery, University of Geneva Hospitals and Faculty of Medicine, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland; ²Department of Radiology, Geneva University Hospitals, University of Geneva Hospitals and Faculty of Medicine, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland; ³Division of Nuclear Medicine, University of Geneva Hospitals and Faculty of Medicine, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland

This report presents a 29-year-old patient with severe temporomandibular joint (TMJ) pain. Anamnesis and clinical examination led us to the diagnosis of TMJ disorder. He was also in control for a malignant paraganglioma originating from the right carotid body. After initial surgery 8.5 years ago and the removal of metastases 2 years ago he was deemed disease free. An ¹⁸F-3,4-dihydroxyphenylalanine (DOPA) positron emission tomography (PET)/CT scan was obtained during follow-up 6 months before he was presented to our clinic. Suspicious of a connection between the actual pain and the tumour, we scrutinized these images. We found a tiny pathological tracer uptake in the right jugular foramen but no correlating finding in the matching CT. We repeated the DOPA PET/CT and found several metastases including the previously detected lesion. Further thin-slice CT and MRI showed a 5 mm paraganglioma located anteriorly to the jugular bulb within the jugular foramen. The lesion was in close relation to the Arnold's nerve, a branch of the vagus nerve which carries sensory information from the external tympanic membrane, external auditory canal and the external ear and explained the severe pain in our patient. He then underwent radiotherapy (45 Gy) during which the pain diminished considerably. In a variety of neuroendocrine tumours, including paraganglioma, DOPA PET/CT allows primary diagnosis, staging and restaging with a higher detection rate than conventional radiological imaging. Owing to low anatomical resolution however, high resolution contrast-enhanced CT and MRI are necessary to complete the investigations.

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Case report

Our colleagues from the otolaryngology department presented us a 29-year-old patient with severe right-sided temporomandibular joint (TMJ) pain. It had started approximately 1 year earlier and the patient had previously consulted several specialists unsuccessfully. On a visual analogue scale, pain intensity was ten out of ten and required oral medication with morphine. The intraoral examination was normal except for considerable tenderness of all insertions of the muscles of mastication and marked tooth abrasions. Extraorally

there was mild bilateral pain on palpation of temporal, masseteric and medial pterygoid muscles and sharp pain on both TMJs. There was no clicking present, no lumps and no asymmetries. A panoramic radiograph was normal. Having seen a faint scar approximately 10 cm long along the anterior part of the right sternocleidomastoid muscle, we resumed our questions. This revealed that the patient underwent surgery for a hereditary paraganglioma (mutation of the genes for succinate dehydrogenase subunit D (SDHD)) of the right carotid body 8.5 years ago. He was well until 2 years ago when paroxysmal blood pressure elevation with concomitant headache occurred. A 24 h blood pressure measurement showed peaks up to 161/113 mmHg and tachycardia up to 131 regular beats per min at the time of headache. Blood tests showed

*Correspondence to: Dr Andrej Terzić, Service of Maxillo-Facial and Oral Surgery, Department of Surgery, University of Geneva Hospitals (HUG), Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland; E-mail: andrej.terzic@hcuge.ch

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elevated catecholamine levels. Contrast-enhanced 1 mm thin-slice CT scans (Somatom Sensation 64, Siemens, Erlangen, Germany) and ¹²³I-metaiodobenzylguanidine (MIBG) scintigraphy (Axis, Philips Healthcare, Eindhoven, Netherlands; 185.8 MBq ¹²³I-MIBG) revealed two mediastinal metastases (para and retrocardiac) and a third metastasis located at the lesser curvature of the stomach. After surgical removal of the three masses, the patient recovered and was deemed disease free. Follow-ups ensued for 2–3 months. After obtaining this information we first treated the obvious bruxism and the TMJ disorder (TMD) with physiotherapy. We gave the patient an appointment 3 weeks later. Following suspicions of a connection to his malignancy, we scrutinized all available notes. We also reviewed all previous radiological exams. An ¹⁸F-3,4-dihydroxyphenylalanine (DOPA) position emission tomography (PET)/CT scan (Biograph Sensation 16, Siemens, Erlangen Germany; 209 MBq ¹⁸F-DOPA) performed 6 months prior to his first consultation in our department (Figure 1) had shown a tiny abnormal radiotracer uptake within the jugular foramen. The matching CT scan however was normal. On recall 3 weeks later, there was absolutely no improvement. So the DOPA PET/CT (Biograph 64, Siemens, Erlangen, Germany; 209 MBq ¹⁸F-DOPA) was urgently repeated (Figure 2) and at this moment showed a sharply circumscribed major uptake of the radiotracer in the jugular foramen. Three more foci of significantly increased tracer accumulation were discovered: in the thoracic spine (Th8 vertebral body); the lumbar spine (L2 vertebral body); and in the retroperitoneum (Figure 2). A contrast-enhanced 0.625 mm thin-slice CT scan (Somatom Sensation 64) (Figure 3) now showed a suspect lesion in the right jugular foramen. Additional MRI (Trio 3 Tesla, Siemens) (Figure 4) was performed to confirm CT and PET/CT findings and to better assess the morphology of the suspected tumour in view of a possible surgical

resection. The MR exam (0.8 mm thin slices of a time of flight (TOF) sequence after intravenous injection of contrast material) was targeted on the area of the jugular foramen and TMJ. It confirmed the presence of a paraganglioma located anteriorly to the jugular bulb within the pars vascularis of the jugular foramen.¹ The additional metastases were confirmed on spine and abdominal MR images (Espree 1.5 Tesla, Siemens). After discussion with the patient, intensity-modulated radiation therapy was performed (45 Gy in 25 fractions of 1.8 Gy with 6 megavolt photons for the neck and 18 megavolt for the other lesions). The pain diminished considerably during treatment.

Discussion

While TMD is a very frequent condition in everyday maxillofacial clinics, paraganglioma remain a rarity.² 90% arise in adrenal glands where they are referred to as pheochromocytoma. The remaining 10% originate from neural crest-derived chromaffin cells outside the adrenal glands—the paraganglion system. Only 3% of all these non-adrenal paraganglioma are located in the head and neck.³ Here, the typical sites are, in descending order, carotid body, vagal body, jugulotympanic region, larynx, nose and paranasal cavities.⁴ In around only 10% of all paraganglioma the tumour is deemed malignant.⁵ Remarkably, the histopathological picture of both the benign and malignant variant are identical. Malignancy is determined only by biological behaviour. In the case of metastasis to non-neuroendocrine tissue, the diagnosis changes from a simple paraganglioma to malignant paraganglioma (MPG).⁶ The reported overall rate for malignancy varies considerably as only a few cases are known. For instance, in carotid body paraganglioma it ranges from 1.4% to 13.5%.^{4,7}

Figure 1 The initial ¹⁸F-3,4-dihydroxyphenylalanine (DOPA) positron emission tomography (PET)/CT image obtained 6 months before presentation reveals a hypermetabolic focus (arrows) in the right jugular foramen on both axial (a) and coronal (b) reformatted fused images

Figure 2 A second ¹⁸F-3,4-dihydroxyphenylalanine (DOPA) positron emission tomography (PET)/CT image obtained shortly after presentation shows an increased size and intensity of the hypermetabolic focus (arrow) on axial cuts at the level of the right jugular foramen (a). The area of pathological radiotracer uptake is located in the anterior portion of the jugular bulb and strongly suggestive of a paraganglioma. Coronal whole-body PET/CT image (b) obtained during the same examination reveals additional hypermetabolic foci (arrows) within the vertebral bodies suggesting paraganglioma metastases

Our patient presented with a MPG involving the pars vascularis of the jugular foramen just anterior to the jugular bulb. The vagus nerve (cranial nerve X) crosses the jugular foramen with the superior vagal (or jugular) ganglion located within the foramen and the inferior vagal ganglion below the skull base. Together with cranial nerve XI, the vagus nerve travels in a common sheath immediately posterolaterally to the inferior

petrosal sinus and anteromedially to the jugular bulb. The first branch of the vagus nerve, the auricular branch or Arnold's nerve, leaves the vagus nerve inside the pars nervosa of the jugular foramen and has its origin in the superior vagal ganglion. It carries sensory information from the external tympanic membrane, external auditory canal and external ear.

By definition, paraganglioma can arise in any site of the paraganglion system. In the jugular area they arise from paraganglia surrounding the jugular bulb, Arnold's nerve or Jacobson's nerve, a branch of cranial nerve IX.^{8,9} Most of these paragangliomas are discovered in an advanced stage with tinnitus, pain and multiple cranial nerve deficits (IX, X, XI) because a significant portion of the jugular foramen is already involved. However, small jugular paragangliomas touching only the jugular ganglion and the nerve of Arnold may present with pain that radiates into the external auditory canal and the TMJ only, as in the patient presented. Even though the lesion measured only 5 mm, its close vicinity to the vagus and Arnold nerve may explain the intense pain experienced by our patient.

The radiological diagnosis of paraganglioma is usually made with thin-slice contrast-enhanced CT and high-resolution MRI with vascular sequences.^{8,9} While CT may demonstrate typical irregular erosions of the jugular foramen in large lesions, MR imaging typically depicts a soft-tissue mass with—if the lesion is large enough—a “salt and pepper appearance”. While “salt” represents slow flow and haemorrhage, “pepper” corresponds to flow voids from large vessels within the mass. In cases with multiple suspected paragangliomas, or when the site is not known, the detection of small lesions in a whole body CT can be very difficult and time consuming. In our case for instance, in CT scans the lesion was only visible in one axial cut and was hard to interpret.

Figure 3 High-resolution contrast-enhanced CT image (0.625 mm thin slices) at the level of the jugular foramen shows the jugular bulb (asterisk) located posteriorly, the internal carotid artery located anteriorly (white arrow) and a small lesion located in the anterior wall of the jugular bulb (black arrow). The lesion appears to enhance less than the adjacent vessels. Note that the bony contours of the jugular foramen are normal

Figure 4 Axial (a) and coronal (b) reformatted images from a contrast-enhanced high-resolution MR vascular sequence (time of flight angiography with 0.8 mm thin slices) show the paraganglioma (dashed arrows) situated in the anterior and superior portion of the jugular vein and bulb (asterisk). The white arrow points at the internal carotid artery. The two arrowheads point at the right temporomandibular joint located in immediate vicinity

In such a case, metabolic imaging is extremely helpful. ¹⁸F-DOPA PET/CT, a recent hybrid anatomometabolic imaging technique, allows primary diagnosis, staging and restaging of a variety of neuroendocrine tumours, including pheochromocytoma and paraganglioma.^{10,11} The detection rate is said to be superior to conventional MIBG scintigraphy¹² and standard ¹⁸F-fluoro-2-deoxy-D-glucose (¹⁸F-FDG) PET/CT. But to what extent this is true is difficult to say. The techniques used are new and data are rare. A recent report in 2009 investigated amongst others the value of CT, MRI, ¹²³I-MIBG scintigraphy, ¹⁸F-FDG, ¹⁸F-DOPA and ¹⁸F-fluorodopamine (¹⁸F-FDA) in patients with malignant and non-malignant paraganglioma.¹¹ It showed that on the one hand it is important if we investigate metastatic or non-metastatic paraganglioma and on the other hand if genotype succinate dehydrogenase subunit B (SDHB) is present or not. The sensitivity compared with MRI and/or CT in metastatic disease is 45% for ¹⁸F-DOPA PET, 57% for ¹²³I-MIBG scintigraphy, 74% for ¹⁸F-FDG PET/CT and

76% for ¹⁸F-FDA PET/CT. In patients with the SDHB subtype of MPG the sensitivity is 20% for ¹⁸F-DOPA PET, 57% for ¹²³I-MIBG scintigraphy, 82% for ¹⁸F-FDA PET/CT and 83% ¹⁸F-FDG PET/CT. But in metastatic non-SDHB patients ¹⁸F-DOPA PET has the highest sensitivity (93%) and is the investigation of choice. Even though ¹⁸F-FDG PET/CT has very good values in this study, it is not recommended for first-line imaging because its uptake is not paraganglioma-specific. Furthermore, the anatomical resolution of PET images is clearly inferior to that of MRI and high-resolution contrast-enhanced CT.^{10,11} So investigations are completed with selective high-resolution CT or MRI.

In conclusion, despite all reported sophisticated techniques, we would like to underline three things in daily routine. First, stay alert even when seeing frequently observed complaints. Second, anamnesis is of crucial importance. And third, if a usually efficient treatment is of absolutely no help, reassess the diagnosis and actively search unusual pathologies.

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