Imaging Pathway of a Pediatric Patient with Succinate Dehydrogenase B-Deficient Paraganglioma

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Pheochromocytoma and paraganglioma are rare in children, at only 1 in every 50,000 cases. Even though some cases are sporadic, they have been connected to syndromes such as von Hippel–Lindau, multiple endocrine neoplasia types IIA and IIB, neurofibromatosis type 1, and hereditary pheochromocytoma–paraganglioma syndromes. A genetic mutation causes around 60% of pheochromocytomas and paragangliomas in children under 18. Methods: A 15-y-old child with a 6-y history of back discomfort is presented. The justification for using 2 functional imaging modalities, 68Ga-DOTATATE PET/CT and 123I-meta-iodobenzylguanidine SPECT/CT, is examined in this case study. We reviewed the patients’ journey since the first referral for imaging. Results: Delaying the molecular imaging modalities has affected patients’ overall diagnosis and applied treatment outcomes. Conclusion: This case study investigates the potential for the earlier use of various diagnostic modalities in conjunction with diagnostic testing to facilitate an earlier diagnosis. However, since this study is based solely on imaging and lacks access to the patient’s clinical or family history, factors such as potential inequities in health-care facilities, health literacy, and socioeconomic status are not addressed. It is essential to acknowledge these influences as they contribute to the inequitable access to health-care settings in New Zealand.

Key Words: neuroendocrine; gallium-68-DOTATATE; molecular biology; paraganglioma; peptide receptor radionuclide therapy; PRRT

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Paragangliomas are neuroendocrine tumors that develop from extraglandular chromaffin nerve cells between the base of the cranium and the pelvis. They are diagnosed more frequently in minors, with an incidence of 0.3 cases per million people per year and a mean age of 11. Boys are typically affected more than girls (1,2). Sympathetic paragangliomas, such as that in this scenario, are believed to originate from paravertebral aorta sympathetic ganglia (3) and are located along the sympathetic chains in the thorax and abdomen (4). Twenty percent of sympathetic paragangliomas are malignant (5). Over 80% of cases of paragangliomas in children are inherited, and more than 20 genes have been implicated in their pathogenesis (6). Depending on the tumor’s size, location, and biochemical activity (3,7), the clinical manifestations of sympathetic paragangliomas may include hypertension, palpitations, migraines, syncope, excessive perspiration, anxiety, and pallor. Approximately 70% of pediatric cases involve persistent hypertension (7).

MATERIALS AND METHODS

The case study highlights the experience of a 15-y-old boy who initially arrived at age 9 with back and hip pain complaints. Shortly after this initial presentation, he was referred for chest, lumbar, and pelvic radiography because of an inexplicable increase in body habitus. Findings were inconclusive, and no further inquiry was conducted until 6 y later, when he presented with rib pain. Extensive imaging and treatments were undertaken after the identification of 2 masses. This communication is a retrospective review of the patient’s journey through the various diagnostic imaging processes, summarized in Supplemental Table 1 (available at http://jnmt.snmjournals.org) and illustrated in Figure 1. Without detailed access to the clinical notes or blood tests, we have summarily hypothesized the reasons for the gaps in the overall process that caused the final diagnosis to be delayed.

Because of the patient’s high body mass index, diagnostic imaging protocols were not adjusted for pediatric sizing. Initial digital radiography was followed by computed radiography, MRI, and lastly functional imaging. A PET/CT scan based on 68Ga-DOTATATE was performed to identify any possible active somatostatin receptor. PET/CT images were acquired 45 min after 159 MBq of 68Ga-DOTATATE had been injected intravenously over 2–3 min at 1.5–2.6 MBq/kg, using 1.5–2.6 MBq/kg rather than a pediatric dose. This dose was adjusted to the patient’s body habitus to acquire diagnostic-quality images. After the PET/CT imaging, a 123I meta-iodobenzylguanidine (123I-MIBG) scan was performed to rule out the possibility of neuroblastomas and pheochromocytomas. Whole-body and SPECT/CT-based 3-dimensional imaging was performed over 2 d after a 30-s 244-MBq 123I-MIBG intravenous injection. Lugol solution was given orally in advance to protect the thyroid from radiation burden.

Both types of functional imaging (68Ga-DOTATATE and 123I-MIBG) showed various positive sites for the disease, with 2 primary locations within the thoracic spine and pelvic areas. Because of the somatostatin receptor–positive scan, the patient was referred for 177Lu-labeled DOTATATE targeted radionuclide therapy.
RESULTS

After the patient presented with worsening symptoms, a chest radiograph highlighted a large occupying mass in the left hemithorax. Subsequent CT of the chest, abdomen, and pelvis and MRI studies showed a significant (16.9 × 11.5 cm) invasive mass protruding within the hemithorax, involving the T6 and T7 vertebral bodies with nearly complete loss of height in both vertebrae, alongside a midline mass in the lower abdomen (13.7 × 10.3 cm) with marked vascularity (Figs. 2–4).

The 68Ga-DOTATATE PET/CT scan indicated that the mass represented succinate dehydrogenase B-deficient metastatic paraganglioma. The 123I-MIBG SPECT/CT confirmed the diagnosis of neuroendocrine tumors, including neuroblastomas and pheochromocytomas. Because of the significant potential for morbidity, surgical intervention was deemed inappropriate by the multidisciplinary team after extensive discussions. The 68Ga-DOTATATE study was undertaken alongside 123I-MIBG to also assess suitability for peptide receptor radionuclide therapy (PRRT) in the absence of viable alternative treatment options. The patient underwent 4 cycles of adult-dose 177Lu-DOTATATE PRRT (7.4 GBq of 177Lu-DOTATATE PRRT per cycle). The posttherapy 68Ga-DOTATATE scan showed signs of stable disease. Despite initial improvement, the patient started to decline after the fourth and final dose, with no significant decrease in the size of the thoracic or pelvic masses.

The case highlights the challenges in managing patients with metastatic neuroendocrine tumors, particularly when surgical intervention is not feasible. PRRT was chosen as an alternative in this case in view of the patient’s clinical condition and lack of viable options. The response to PRRT was encouraging initially, with improvement in the patient’s mobility and quality of life. However, the final outcome was less
successful than anticipated, with no significant decrease in the size of the masses.

The case also highlights the limitations in accessing certain treatment modalities in some regions, such as the unavailability of $^{123}$I-MIBG therapy in New Zealand. This limitation underscores the importance of global collaboration and access to advanced medical treatments for patients with complex medical conditions.

**DISCUSSION**

The best outcomes for treatment are based on early detection of as many lesions as possible (8). In addition, precise localization of lesions is vital for treatment decisions so that the effects of radiation therapy are minimized (9). The literature is consistent that CT and MRI are highly sensitive for localized tumors, at 95%–100% sensitivity, but drop to 45% sensitivity for metastases (10). Therefore, functional imaging is preferred when metastases are suspected, as when 2 tumors were found.

$^{18}$F-FDG and $^{18}$F-FDOPA are often used for skeletal tumors (10) and, before 2015, were regarded as the tracers of choice for metastatic paragangliomas. However, comparative studies (11) have shown the superiority of $^{68}$Ga-DOTATATE in the localization of succinate dehydrogenase subunit-related paragangliomas in pediatric patients and early detection of metastatic disease. Therefore, the literature (12) supports its use in pediatric imaging, for which it is superior in detecting sporadic and metastatic paragangliomas. However, the normal physiologic adrenal uptake reduces sensitivity to pheochromocytomas. Therefore, contrast medium is suggested for abdominal scans (11).

Because $^{123}$I-MIBG targets catecholamine, entering the cell via the norepinephrine transporter, Mettler and Guibertau (10,13) make a case that $^{123}$I-MIBG is more sensitive for pheochromocytomas and neuroblastoma, with sensitivities of 85%–100%. It is the most widely used functional imaging technique for assessing adrenal pheochromocytomas and sympathetic paragangliomas but has a minimal role for the head and neck. Sensitivity for thoracic paraganglioma is too low (56%–78%), resolution is limited, and quantitative uptake estimates have not yet been provided (13). Although PET/CT is associated with a higher diagnostic accuracy, better patient compliance and comfort, and lower radiation exposure, SPECT/CT has a proven incremental value in assessing neuroendocrine neoplasms (14). Therefore, it is concluded that $^{123}$I-MIBG was chosen to complement $^{68}$Ga-DOTATATE to provide a breadth of coverage for both pheochromocytomas and paragangliomas.

Babic et al. (15) recommend that all pediatric patients with paragangliomas undergo genetic testing and imaging to detect metastatic disease and guide treatment, as 80% of patients have a germline mutation in a known susceptibility gene. Funded gene tests for hereditary paragangliomas are available throughout New Zealand to identify the most common succinate dehydrogenase...
gene mutations (16). Because sympathetic parangliomias are characterized by a catecholamine excess, there is a 24-h urine test and blood plasma test for measuring free metanephrines (a metabolite of catecholamine) released from the tumor (17). Bolah and Bunchman (18) advocate localization of tumors with imaging only once paranglioma is suspected and only once this biochemical evidence is established. These susceptibility tests have very few false-negative results. Elevations of 4-fold or more above the reference level are associated with a nearly 100% probability of a catecholamine-secreting tumor and might have been considered in this case.

The time to diagnosis is influenced by tumor growth rate and clinician awareness. There is a 4.5-y gap in imaging in this case study. Paranglioma is an excellent mimic, with the differential diagnosis a challenge, typically taking 4 or more years (17,19). Michałowska et al. (19) describe succinate dehydrogenase subunit–based parangliomias as slowly growing tumors with a thoracic volume doubling time of 11.8 y, contrasting with this case. The Royal New Zealand College of General Practitioners recognizes the challenge of low awareness of rare disorders (https://www.rarediseases.org.nz/assets/VOICE-OF-RARE-DISORDERS-White-Paper-February-2021-FINAL.pdf). However, the New Zealand Guidelines Group (20) lays out clear screening guidelines for general practice, supported internationally (21), when it comes to young people and cancer. CT/MRI, because of accessibility, will often be the first detailed diagnostic imaging technique used, but initial diagnosis using standard radiographs should not be underestimated, as the radiograph at 15 y shows. For pediatrics, radiographs offer a balance in radiation protection. When done regularly, they are safer than the radiation burden of CT and cheaper and more practical for pediatrics than MRI. CT and MRI are more sensitive for pediatric tumors with suspicion of something abnormal, but functional imaging is essential where metastases are suspected (22).

In addition to imaging modalities, nuclear medicine can be used to treat pediatric paranglioma. 131I, for example, can be utilized to administer targeted radiation therapy to cancer cells while causing minimal damage to healthy cells. Radioisotope therapy, or targeted radionuclide therapy, is a method that has been shown to help treat juvenile paranglioma, especially when combined with other treatments such as surgery and chemotherapy (23,24). Molecular imaging is another method by which nuclear medicine can enhance health outcomes for children with paranglioma. With PET and SPECT, it is possible to find out what chemicals or receptors are on the surface of cancer cells. By using radiotracers to target these molecules or receptors, healthcare providers can develop images that reveal precise information about the biology of the tumor and how it responds to treatment. With this information, treatment plans can be tailored to fit the needs of each patient, making the treatments more effective and reducing the chance of side effects. Molecular imaging can also be used to find possible targets for new therapies (25), making it easier to treat pediatric paranglioma and other types of cancer. Finally, nuclear medicine is essential in diagnosing, treating, and monitoring pediatric paranglioma. Using imaging tools and custom radionuclide therapy, doctors can find and treat this rare cancer early. Also, molecular imaging can tell us a lot about the biology of the tumor, which can help us come up with new treatments and make the ones we already have work better (26,27).

Integration of clinicopathologic information with imaging is essential for early diagnosis. Access to the clinical records is necessary for what was performed and is a limitation to this analysis. However, on the basis of available data and the literature, there may have been a missed opportunity to diagnose these rapidly growing tumors earlier. Therefore, a traditional, holistic approach should be adopted, combining guidelines with best-practice testing to avoid missing rare disorders. Consultation with tertiary or quaternary centers is also recommended in atypical cases. Annual functional imaging is recommended for the patient. In addition, a thorough family history check, particularly of siblings, is recommended.

Several significant factors likely contributed to the delay in diagnosis. First, there was reduced accessibility due to the patient’s remote geographical location. There were also patient comorbidities making it difficult for the patient to communicate symptoms and their escalation. Lastly, functional imaging is available in only a few centers in the country, with 68Ga-DOTATATE PET/CT in only one, and at the outset, 123I-MIBG was available only overseas, which, when combined with complex pathways to access specialist imaging, resulted in significant delays (27). In contrast to these delays, once the tumors were identified, however, this paucity of information was replaced with a rapid and intensive access to a range of high-quality specialist services and treatments.

CONCLUSION

Some tumors may have been discovered earlier as a result of earlier use of genetic and blood testing. Clinically, despite its unusually quick growth, sympathetic parangliomas show a wide range of symptoms and back discomfort. Potentially earlier detection may also have been achieved by following existing primary-care guidelines (26,27), which recommend when to refer to specialists as well as the correct integration of all clinical history and imaging data and biomarkers. An earlier use of specialist instigated nuclear imaging may then have made it possible to allow surgical intervention as a viable option.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.
KEY POINTS

QUESTION: What are the potential challenges in diagnosing paragangliomas in pediatric patients, and how can early detection be improved?

PERTINENT FINDINGS: Diagnosing paragangliomas in pediatric patients can be challenging for various reasons. One challenge is the rarity of the condition, making it difficult for doctors to recognize its symptoms and differentiate it from other conditions. Additionally, the slow-growing nature of some paragangliomas may lead to delayed diagnosis, as symptoms may not be apparent until the tumor reaches a significant size. The lack of awareness among health-care providers about this rare condition may also contribute to delays in diagnosis.

IMPLICATIONS FOR PATIENT CARE: To improve early detection, it is crucial for pediatric patients to undergo regular screenings and check-ups. Genetic testing and imaging should be considered, especially if there is a family history of paragangliomas or other neuroendocrine tumors. These tests can help identify potential risks and facilitate early intervention.

REFERENCES