2020

Gastrointestinal neuroendocrine tumors in Fontan patients

Corey Vural
Washington University School of Medicine in St. Louis
Priya Skaria
Washington University School of Medicine in St. Louis
Louis P. Dehner
Washington University School of Medicine in St. Louis
Geetika Khanna
Washington University School of Medicine in St. Louis

Radiology Case Reports 15 (2020) 2153–2156

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

Gastrointestinal neuroendocrine tumors in Fontan patients ☆

Corey Vural, BA[a], *Priya Skaria, MBBS*[b], *Louis P. Dehner, MD*[b], *Geetika Khanna, MD, MS*[c,*]

[a] *Washington University School of Medicine, Campus Box 8131, 510 S. Kingshighway, St Louis, MO 63110 USA*
[b] *Department of Pathology, Washington University School of Medicine, St Louis, MO, USA*
[c] *Mallinckrodt Institute of Radiology, Washington University School of Medicine, St Louis, MO, USA*

ARTICLE INFO

Article history:
Received 27 May 2020
Revised 31 July 2020
Accepted 1 August 2020

Keywords:
Fontan procedure
Neuroendocrine tumors
Pancreas
Jejunum

ABSTRACT

The Fontan procedure used for palliation of single ventricle physiology is associated with multisystemic morbidity. With improving survival and increased use of surveillance imaging in this patient population, long-term complications associated with Fontan circuits are commonly encountered by radiologists. One interesting observation is the apparent increased risk of paragangliomas and pheochromocytomas in this group of patients and perhaps a pathogenetic role of chronic hypoxia. We report 2 cases of gastrointestinal neuroendocrine tumors (NET) in the setting of Fontan circuit. The first is a 20-year-old female with history of hypoplastic left heart and Fontan palliation who presented with hematochezia and was diagnosed with a jejunal grade 2 NET. The second case is of a 12-year-old boy with history Fontan palliation for single ventricle physiology, incidentally found to have a well-differentiated pancreatic NET during precardiac transplant workup. These cases should alert the radiologists to be aware of the apparent association between Fontan procedure and NET.

Introduction

The Fontan procedure is a widely applied surgical approach for the palliative management of congenital heart diseases with single ventricle physiology such as hypoplastic left heart and double outlet right ventricle [1]. It involves a 2-stage cavopulmonary bypass with routing of the systemic venous return to the pulmonary circuit while bypassing the single pumping ventricle. In the process, there is elevated systemic venous pressures, chronic hypoxia, and impaired lymphatic drainage. Over the last 4 decades, there has been significant improvement in the survival of these patients with a reported 20-year survival of up to 85% [1,2]. With improved survival, long-term morbidities associated with a cavopulmonary bypass have emerged, for which the radiologists should be aware in their imaging examination for the multisystemic complications of the Fontan palliation [3].

This report documents our experience with 2 patients who had the Fontan procedures. They developed gastroin-

☆ Need for consent was waived by the institutional review board.

* Corresponding author.
E-mail address: khannag@wustl.edu (G. Khanna).

https://doi.org/10.1016/j.radcr.2020.08.004

testinal and pancreatic neuroendocrine tumors (NETs), the first to our knowledge. These cases now join the other NETs, pheochromocytomas and paragangliomas, previously reported in this patient population [5].

Case 1

A 20-year-old female with history of hypoplastic left heart syndrome, status post Fontan palliation at 3 years of age, presented with lower gastrointestinal bleeding and dizziness which progressed to hematochezia. Computed tomography (CT) of the abdomen and pelvis showed active contrast extravasation at the duodenojejunal junction with an intraluminal jejunal mass and enlarged mesenteric lymph nodes (Fig. 1a–c). Exploratory laparotomy revealed a vascular mass at the base of the mesentery and a proximal jejunal mass. A jejunal resection with duodenal-jejunal anastomosis was performed (Fig. 1d). The ulcerated jejunal mass was a well-differentiated NET grade 2 (5% Ki67 index), with lymph node involvement (T2N1M0) (Fig. 1e and f).

Case 2

A 12-year-old boy was referred for cardiac transplantation evaluation; he had a history of a single ventricle physiology including transposition of great vessels, right ventricle dominant unbalanced arterioventricular canal and mixed total anomalous pulmonary venous connections. His palliative surgery included a lateral tunnel Fontan conduit at the age of 6 years. As part of the pretransplant evaluation he underwent a contrast enhanced CT of chest, abdomen, and pelvis which showed an exophytic, enhancing lesion arising from the pancreas (Fig. 2a and b). Follow-up magnetic resonance imaging confirmed a diffusion-restricting enhancing retroperitoneal lesion and a NET was suspected (Fig. 2c and d). CT-guided biopsy of the lesion showed a well-differentiated neuroendocrine tumor with Ki67 index <3% and no mitotic figures/nuclear atypica (Fig. 2e and f). Based on the characteristics of the lesion on imaging and its low-grade features, it was determined that the risk of metastasis was extremely low and the decision was made to perform an orthotopic cardiac transplantation.

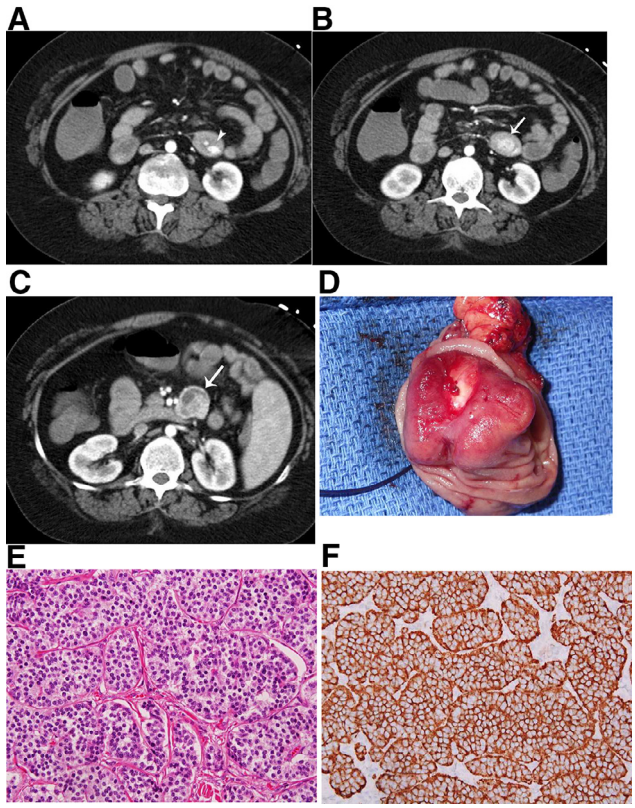

Fig. 1 – A 20-year-old female with history of hypoplastic left heart presented with lower gastrointestinal bleeding. (a-c) Contrast enhanced CT of the abdomen and pelvis shows active extravasation of contrast into the proximal jejunum (arrowhead) with an intraluminal hyper enhancing mass (arrow) and enlarged enhancing retroperitoneal lymph nodes (arrow). (d) Surgical specimen from exploratory laparotomy shows the hypervascular endoluminal mass within the resected jejunum, (e) Hematoxylin and eosin stain photomicrograph (400× magnification) shows nests of tumor composed of uniform tumor cells with low-grade nuclear features and minimal mitotic activity, (f) chromogranin stain (400× magnification) shows diffuse cytoplasmic secretory granules positive for chromogranin confirming a diagnosis of neuroendocrine tumor.

Discussion

We report 2 patients who had Fontan procedures in early childhood for single ventricle physiology cyanotic congenital heart disease who presented with gastrointestinal NETs at the ages of 20 and 12 years. These cases are unique in that these tumors expand the spectrum of NETs in this clinical setting as prior reported tumors have included predominantly pheochromocytomas and paragangliomas.

The first case series reporting an association between cyanotic congenital heart disease and pheochromocytomas dates to 1964 [4]. This series included 5 cases and 2 of these patients were children [6]. In a more recent study of 283 Fontan patients, Song, et al, reported 3 cases of pheochromocytomas and 4 paragangliomas with 3 of the 7 patients 18 years of age or younger [5]. Three of these patients were clinically asymptomatic, while 4 had symptoms such as hypertension, headache and palpitations. The authors suggested that the NETs, pheochromocytomas and paragangliomas, occurred more often in this young Fontan age group than in the general population. Later, Opotowsky et al, have shown an increased risk of pheochromocytomas and paragangliomas in those with cyanotic congenital heart disease as compared to noncyanotic congenital heart disease (odds ratio 6.0 and 95% confidence interval: 2.6-13.7) in an international consortium study [6]. In their series, 50% of the 20 cases with a NET in the

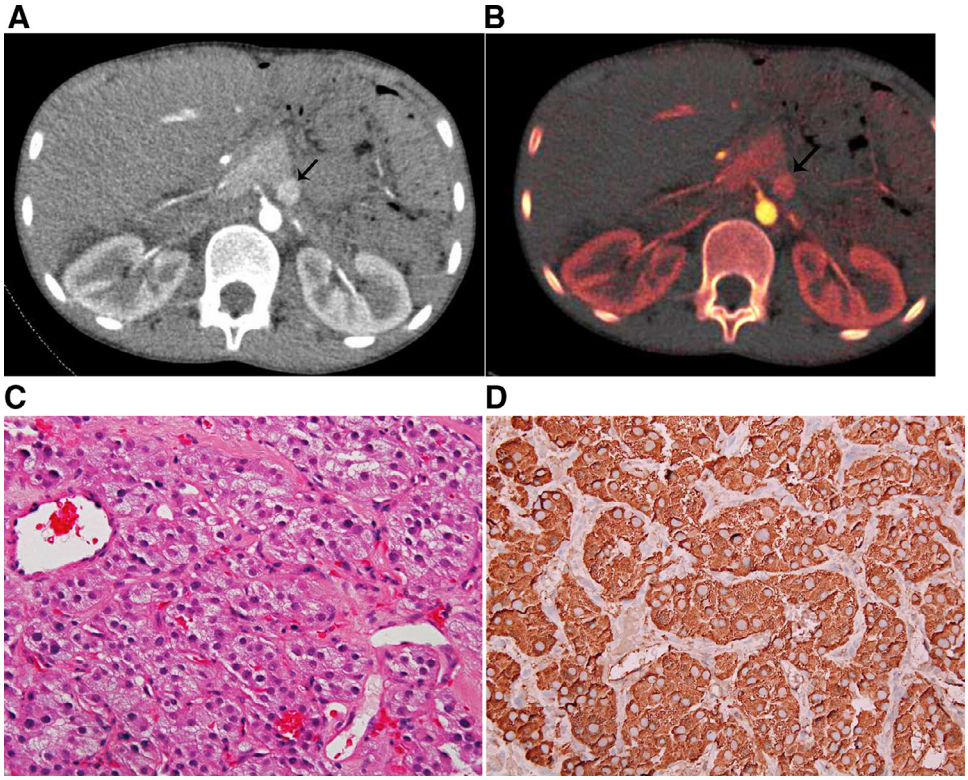

Fig. 2 – A 12-year-old boy with incidentally detected pancreatic mass. (a) Contrast enhanced CT in arterial phase and corresponding iodine map (b) show an avidly enhancing retroperitoneal mass arising from the body of the pancreas. (c) Hematoxylin and eosin stain photomicrograph (400 x magnification) shows nests of tumor composed of uniform tumor cells with low-grade nuclear features and minimal mitotic activity, (d) chromogranin stain (400 x magnification) shows diffuse cytoplasmic secretory granules positive for chromogranin confirming a diagnosis of neuroendocrine tumor.

setting of cyanotic congenital heart disease had undergone a cavopulmonary shunt. They also showed a younger age at diagnosis (median age of 31.5 years; 3/15 cases ≤18 years of age) of NETs with cyanotic congenital heart disease and approximately 40% of patients had multiple tumors.

The exact pathogenesis for the increased incidence of NETs in the Fontan population is unclear and with its age group predilection, it has been suggested that a chronic state of hypoxia is a risk factor. This hypothesis is supported by the fact that genetic factors associated with increased incidence of NETs such as succinate dehydrogenase complex mutations and von Hippel Landau are associated with activation of the hypoxia inducible factor. Mutations in the hypoxia pathway are manifested by a noradrenergic phenotype (elevated norepinephrine and metanephrines) and absence of adrenergic phenotype (normal epinephrine and metanephrines) [5]. Folger et al, also postulated that a state of chronic hypoxia may result in adrenal medullary hyperplasia and increased incidence of adrenal tumors [4]. An increased incidence of pheochromocytomas and paragangliomas has also been shown in those populations living at high altitudes as circumstantial support for the hypoxia theory. Hence, paragangliomas, pheochromocytomas and related tumors have been characterized as so-called pseudohypoxic tumors [7].

With improving lengths of survival of Fontan patients, radiologists are more likely to encounter complications of Fontan physiology on imaging beyond the pulmonary and hepatic abnormalities [8]. Specifically, abdominal radiologists should be aware of the gastrointestinal, adrenal, and retroperitoneal morbidity associated with a Fontan circuit. Abdominal imaging surveillance to evaluate for Fontan complications such as cardiac cirrhosis, focal liver masses, lymphatic leaks, and protein losing enteropathy is now part of the standard surveillance of this patient population [9]. Hence, NETs may be detectable incidentally as in our second case or with life-threatening symptoms such as in our case 1.

In summary, we have described 2 cases of NETs of the gastrointestinal system in the setting of Fontan palliation. These patients can present with symptoms related to the hypervascular tumors or the tumors may be detected incidentally. Abdominal radiologists should be aware of this association, especially given the improved survival of Fontan patients and increasing use of surveillance imaging in this patient population.

REFERENCES

[1] d'Udekem Y, Iyengar AJ, Cochrane AD, Grigg LE, Ramsay JM, Wheaton GR, et al. The Fontan procedure: contemporary techniques have improved long-term outcomes. Circulation 2007;116(11 Suppl):I157–64.

[2] Pundi KN, Johnson JN, Dearani JA, Pundi KN, Li Z, Hinck CA, et al. 40-Year follow-up after the fontan operation: long-term outcomes of 1,052 patients. J Am Coll Cardiol 2015;66(15): 1700–1710.
[3] Fredenburg TB, Johnson TR, Cohen MD. The Fontan procedure: anatomy, complications, and manifestations of failure. Radiographics 2011;31(2):453–63.
[4] Folger GM Jr, Roberts WC, Mehrizi A, Shah KD, Glancy DL, Carpenter CC, et al. Cyanotic malformations of the heart with pheochromocytoma. A report of five cases. Circulation 1964;29:750–7.
[5] Song MK, Kim GB, Bae EJ, Lee YA, Kim HY, Min SK, et al. Pheochromocytoma and paraganglioma in Fontan patients: common more than expected. Congenit Heart Dis 2018;13(4):608–16.
[6] Opotowsky AR, Moko LE, Ginns J, Rosenbaum M, Greutmann M, Aboulhosn J, et al. Pheochromocytoma and paraganglioma in cyanotic congenital heart disease. J Clin Endocrinol Metab 2015;100(4):1325–34.
[7] Cerecer-Gil NY, Figuera LE, Llamas FJ, Lara M, Escamilla JG, Ramos R, et al. Mutation of SDHB is a cause of hypoxia-related high-altitude paraganglioma. Clin Cancer Res 2010;16(16):4148–54.
[8] Khanna G, Bhalla S, Krishnamurthy R, Canter C. Extracardiac complications of the Fontan circuit. Pediatr Radiol 2012;42(2):233–41.
[9] Rychik J, Atz AM, Celermajer DS, Deal BJ, Gatzoulis MA, Gewillig MH, et al (2019) Evaluation and management of the child and adult with fontan circulation: a scientific statement from the American Heart Association. Circulation:CIR0000000000000696.