Acute Cardiac Complications and Subclinical Myocardial Injuries Associated with Pheochromocytoma and Paraganglioma

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Abstract

Background: Catecholamine excess arising from pheochromocytomas and paragangliomas (PPGLs) can cause a wide spectrum of cardiac manifestations, including acute cardiac complications (ACCs) and subclinical myocardial injuries (SMIs). Hence, we aimed to conduct a comprehensive analysis of ACCs and SMIs in a large cohort of PPGLs.

Methods: We retrospectively analyzed the clinical data of consecutive patients with PPGLs admitted between January 2013 and July 2020 (n = 189). The prevalence and presentation of ACCs and SMIs were investigated, and comparisons were conducted between cases with and without ACCs.

Results: Fourteen patients (7.4%) fulfilled the criteria for ACCs, consisting of nine cases (4.8%) with Takotsubo-like cardiomyopathy, three cases (1.6%) with heart failure with preserved ejection fraction, and the remaining one (0.5%) with catecholamine-induced cardiomyopathy. Compared to those without ACCs (n = 175), patients with ACCs had higher prevalence of epinephrine-producing PPGLs (81.8% vs 33.9%, $P = 0.006$), and were more likely to show invasive behavior (61.5% vs 27.3%, $P = 0.022$) and hemorrhage/necrosis (53.9% vs 17.4%, $P = 0.005$) at histology. Among patients suffered Takotsubo-like cardiomyopathy, an apical sparing pattern (5/7, 71.4%) dominated in the impaired patterns of longitudinal strain (LS). In the end, a fairly high percent (21/77, 27.2%) of patients (excluding 14 cases with ACCs) who underwent screening troponin, natriuretic peptide, and echocardiography had SMIs.

Conclusions: One in every fourteen PPGLs patients presented with ACCs; and, in the cases with Takotsubo-like cardiomyopathy, an apical sparing pattern was the primary pattern in LS. Furthermore, nearly one-third of patients without symptoms had SMIs. The diagnosis of PPGLs should be considered in patients with acute reversible cardiomyopathy, especially with an apical sparing pattern in LS.

Background

Pheochromocytomas (PHEOs) and paragangliomas (PGLs) (PPGLs) are rare tumors, secreting catecholamines (CAs), and have a wide variety of cardiovascular manifestations and complications, which were reviewed recently[1]. Clinically, the presentations of PPGLs are usually unspecific, and only a limited proportion of patients display classic triad of headache, palpitation and sweating, resulting in the delay in diagnosis, especially in cases with cardiac complications[2, 3]. Acute cardiac complications (ACCs) due to excess amount of CA, including epinephrine, norepinephrine, and sometimes dopamine, in patients with PPGLs may be life-threatening, and timely diagnosis and surgery can be life-saving[1]. To date, only a few retrospective series of PPGLs were reported from cardiac perspectives, revealing the prevalence of ACCs varying from 11–19.3% [4–8].

ACCs related to PPGLs encompass arrhythmias (bradycardia and tachycardia), Takotsubo-like cardiomyopathy, dilated cardiomyopathy, thromboembolism, acute coronary syndrome, and so on[1]. PPGLs are considered as secondary causes of Takotsubo syndrome (TTS) in the ESC expert consensus, and dozens of cases have been reported[3, 9].

In the current study, we retrospectively reviewed the patients diagnosed with PPGLs in our center and screened carefully for patients with ACCs. The prevalence, features and outcomes of PPGLs patients with ACCs were accessed; furthermore, comparisons between patients with and without ACCs were conducted aimed to disclose the patients' features associated with ACCs. Additionally, subclinical myocardial injuries (SMIs) were also investigated to reveal the CAs-induced cardiac damage without causing clinical symptoms.

Methods

Study populations

Consecutive patients, diagnosed with PPGLs (clinical or histopathological diagnoses), admitted between January 2013 and July 2020, were included for analysis. Clinical diagnoses were established by classic CAs-related paroxysmal complaints (headache, palpitations, and/or profuse sweating) in combination with adrenal tumors with features suggestive of PPGLs on computed tomography (CT) or magnetic resonance imaging (MRI) scan and elevated plasma CAs or metanephrine (MN) / normetanephrine (NMN) (MNs) at least two times the upper limit of normal (ULN)[10]. Finally, only four patients were clinically diagnosed with PPGLs, and the remaining 185 cases were proven by histopathology.

Clinical assessments

Data on demographic factors, patterns of hypertension, clinical presentations, electrocardiogram (ECG) alterations, biochemical examinations, pre-operative plasma CAs and MNs levels, echocardiography results, characteristics of tumors, and in-hospital outcomes were recorded. The patterns of hypertension involved normal, sustained (just as essential hypertension), paroxysmal (paroxysms of hypertension on a background of normal blood pressure), mixed (paroxysms of hypertension on a background of sustained hypertension) and unknown pattern[2].

Hypertension was based on the diagnosis at admission and pre-operative blood pressure readings, as blood pressure might drop after surgery. We categorized the patterns of tumor secretion into being epinephrine predominant ($\geq 2 \times$ ULN, including MN), norepinephrine predominant ($\geq 2 \times$ ULN, including NMN), and a combination of both[4]. Maximal tumor diameters were comprehensively determined by gross pathological specimens and pre-operative CT/MRI. The estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI method[11].

The diagnoses of ACCs were established in the presence of at least one of the following clinical situations before surgery: 1) Takotsubo-like cardiomyopathy diagnosed by the following combination[9]: I) transient left ventricular dysfunction with wall-motion abnormality extending beyond a single epicardial coronary artery distribution; II) absence of significant coronary artery stenosis confirmed by coronary artery angiography (CAG) or coronary computed tomography angiography (CTA), or without risk factors and history of angina; III) ECG abnormalities or elevated cardiac biomarkers; IV) no evidence of viral infection; 2) heart failure with unknown etiologies, which was most likely attributed to a CAs release from PPGLs, requiring hospitalizations or intravenous diuretic therapy; 3) thromboembolism events most likely of cardiac origin, arrhythmias requiring hospitalizations or antiarrhythmic therapy, and any other cardiac events which were believed to be related with PPGLs.

In addition, SMIs were assessed to reveal detectable myocardial insults before surgery without heart-related symptoms. SMIs were defined as any identified abnormality in myocardial injury biomarkers (high-sensitivity cardiac troponin T), N-terminal pro-B type natriuretic peptide (NT-proBNP), and systolic dysfunction using two-dimensional (2D) strain analysis in the absence of overloading or other conditions which could alternatively explain the abnormal findings.

In suitable patients, 2D strain analysis was offline performed by a single experienced examiner (Y.X. Miu) using dedicated software (EchoPAC, Norway) and data on parameters including global longitudinal strain (GLS), impaired patterns of longitudinal strain (LS) (e.g., apical, apical sparing which means midventricular or basal strain impairment, segmental, and global) and any other valuable information were documented.

All patient records were anonymized before analysis and the Institutional Review Boards (IRB) waived the requirement for informed consent due to the retrospective nature of the study. The study protocol was approved by the IRB of Soochow University and followed the principles of the Helsinki Declaration.

Statistical analysis

Continuous variables were assessed for normality by Skewness/kurtosis test and expressed as mean $\pm$ standard deviation (SD) or median (25th, 74th percentage), as appropriate. Means were compared using 2-tailed Student t-test or, in the case of nonnormality, Ranksum test. Categorical variables were shown as numbers (percentages) and differences were detected using Pearson chi-square test or Fisher's exact test, where appropriate. All analyses were carried out using STATA version 14.0 (Stata Corp, College Station, TX). Two-tailed *P* value less than 0.05 was considered statistically significant.

Results

As shown in Table 1, a total of 189 cases were included for analysis, among whom median age was 53 (38, 62) years and of whom 52.9% (100/189) were female. Surprisingly, PPGLs were incidentally found in 59.3% (112/189) of patients, among whom no symptoms occurred or, in symptomatic cases, symptoms were not considered to be related to space-occupying effect of tumors or CAs-related effect (data not shown). Hypertension occurred in 97 (51.3%) subjects, and sustained pattern (52/97, 53.6%) dominated over paroxysmal (15/97, 15.5%), mixed (19/97, 19.6%), and unknown (11/97, 11.3%) pattern. With regard to symptoms documented in medical records, abdominal discomfort (nausea or vomiting), chest pain, dyspnea and classic triad symptoms (headache, palpitation, and/or profuse sweating) appeared in 9.5% (18/189), 3.2% (6/189), 14.8% (28/189) and 8.5% (16/189) of included subjects, respectively. Troponin (55/189, 29.1%) and NT-proBNP (51/189, 27.0%) were tested in only approximately one-quarter of study subjects, perhaps due to that only patients suspicious of cardiac damage were screened. 70 (37.0%) patients were screened for CAs secretion of tumors, as plasma CAs/MNs test was unavailable until January 2018 in our center; however, urine vanillylmandelic acid test was performed in 103 (54.5%) cases, resulting in 135 (71.4%) patients undergoing at least one of the aforementioned endocrine tests. The majority of patients received urine routine examination (185/189, 97.9%), ECG examination (182/189, 96.3%), blood count examination (187/189, 98.9%), and renal function examination (188/189, 99.5%). Of note, invasive behavior and the presence of hemorrhage/necrosis on pathology reports were described in 29.7% and 20.0% of subjects, respectively.

Table 1
Clinical profiles of patients diagnosed with PPGLs and comparisons between ACCs group and non-ACCs group.

	All (n = 189)	non-ACCs (n = 175)	ACCs (n = 14)	<i>P value</i>
Male	89 (47.1)	79 (45.1)	10 (71.4)	0.058
Age (years)	53 (38, 62)	54 (38, 62)	48 (38, 52)	0.320
History of hypertension	97 (51.3)	86 (49.1)	11 (78.6)	0.034
Patterns of hypertension (n = 97)				0.266
sustained	52 (53.6)	49 (57.0)	3 (27.3)	
paroxysmal	15 (15.5)	13 (15.1)	2 (18.2)	
mixed	19 (19.6)	15 (17.4)	4 (36.4)	
unknown	11 (11.3)	9 (10.5)	2 (18.2)	
Symptoms				
nausea or vomiting	18 (9.5%)	11 (6.3)	7 (50.0)	< 0.001
presence of chest pain	6 (3.2)	4 (2.3)	2 (14.3)	0.065
presence of dyspnea	28 (14.8)	14 (8.0)	14 (100)	< 0.001
presence of triad ^{&}	16 (8.5)	15 (8.6)	1 (7.1)	1.000
ECG changes (n = 182)				
ST-segment changes	19 (10.4)	15 (8.9)	4 (28.6)	0.043
T wave inversion	29 (15.3)	22 (13.1)	7 (50.0)	0.002
Blood parameters				
hemoglobin (g/L) (n = 187)	132.8 ± 20.7	132.5 ± 20.2	136.8 ± 26.4	0.452
platelet count (× 10 ⁹ /L) (n = 187)	256.1 ± 81.5	251.9 ± 76.6	308.6 ± 118.5	0.100
white blood cell count (× 10 ⁹ /L) (n = 187)	6.6 (5.5, 8.6)	6.4 (5.4, 8.1)	15.6 (12.1, 18.9)	< 0.001
eGFR (ml/min/1.73 m ²) (n = 188)	108.0 (96.9, 117.8)	108.0 (97.4, 117.8)	106.1 (49.3, 117.3)	0.408
Positive urine protein (n = 185)	24 (13.0)	19 (11.1)	5 (35.7)	0.026
Cardiac biomarkers				
elevation of troponin (n = 55)	19 (34.5)	6 (14.3)	13 (100)	< 0.001
elevation of NT-proBNP* (n = 51)	20 (39.2)	7 (18.4)	13 (100)	< 0.001
Patterns of secretion (n = 70)				
unknown	4 (5.7)	4 (6.8)	0 (0)	
without endocrine	12 (17.1)	12 (20.3)	0 (0)	0.044
epinephrine predominant	5 (7.1)	4 (6.8)	1 (9.1)	
norepinephrine predominant	25 (35.7)	23 (39.0)	2 (18.2)	

Continuous variables are expressed as mean ± standard deviation or median (25th, 75th percentage); categorical variables are presented as number and percentages in parentheses. Missing data varied by variables.

Abbreviations: ACCs: acute cardiac complications; cm: centimeter; ECG: electrocardiography; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro-B type natriuretic peptide.

[&]defined as presentation of headache, palpitation, and/or profuse sweating.

*defined as NT-proBNP on admission equal to or greater than 125 pg/ml.

	All (n = 189)	non-ACCs (n = 175)	ACCs (n = 14)	<i>P value</i>
a combination of both	24 (34.3)	16 (27.1)	8 (72.7)	
Patterns of secretion (n = 70)				
epinephrine secretion	29 (41.4)	20 (33.9)	9 (81.8)	0.006
Tumor characteristics				
paragangliomas	52 (27.5)	50 (28.6)	2 (14.3)	0.357
bilateral adrenal tumors (n = 137)	6 (4.4)	5 (4.0)	1 (8.3)	0.429
right adrenal tumors (n = 137)	70 (51.1)	64 (51.2)	6 (50.0)	0.937
maximal tumor diameters (cm)	4.5 (3.2, 6)	4.5 (3, 6)	5.5 (4.7, 6.5)	0.053
invasive behavior at histology (n = 185)	55 (29.7)	47 (27.3)	8 (61.5)	0.022
hemorrhage/necrosis at histology (n = 185)	37 (20.0)	30 (17.4)	7 (53.9)	0.005
Continuous variables are expressed as mean $\pm$ standard deviation or median (25th, 75th percentage); categorical variables are presented as number and percentages in parentheses. Missing data varied by variables.				
Abbreviations: ACCs: acute cardiac complications; cm: centimeter; ECG: electrocardiography; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro-B type natriuretic peptide.				
&defined as presentation of headache, palpitation, and/or profuse sweating.				
*defined as NT-proBNP on admission equal to or greater than 125 pg/ml.				

Acute cardiac complications

As depicted in Table 2, fourteen (7.4%) patients suffered ACCs, including nine cases (4.8%) with Takotsubo-like cardiomyopathy, three cases (1.6%) with heart failure with preserved ejection fraction (HFpEF) and one case (0.5%) with catecholamine-induced cardiomyopathy. Two patients displayed recurrent episodes of Takotsubo-like cardiomyopathy, of whom one (case 10, two times) with 2 years apart and one (case 9, three times) with 4 years apart. Predisposing factors were identified in only six (42.9%) cases, consisting of physical activity or defecation in three cases, operation in one, pregnancy in one and respiratory tract infection in the remaining one. In addition, labile blood pressure was detected in five patients (35.7%). As for the location of the tumors, diagnoses of PGLs were made in only two cases. In the eleven patients who were screened for plasma catecholamine levels, the pattern of a combination of both (8/11, 72.7%) dominated over the pattern of epinephrine predominance (1/11, 9.1%) and norepinephrine predominance (2/11, 18.2%). All thirteen patients with biomarkers for cardiac injuries displayed elevated troponin T (median 437.6 pg/ml) and NT-proBNP (median 8946 pg/ml). The mean of left ventricular ejection fraction (LVEF) in acute phase was 0.45, with a range of 0.21–0.65; notably, the LVEF reached the normal range by 6–30 days in all nine patients diagnosed with Takotsubo-like cardiomyopathy. Due to the familial PHEOs and other endocrine glands involvement, case 4 was diagnosed with multiple endocrine neoplasia type 2 without genetic testing. Case 14 was a mid-aged male patient and underwent re-echocardiography examination at 10 months after surgery, which showed no recovery of LVEF, leading to the diagnosis of catecholamine-induced cardiomyopathy.

Table 2
Characteristics of patients with ACCs.

Case	Sex/age (years)	Initial symptoms	Triggers	Labile blood pressure	Location of tumors	Plasma catecholamine (× ULN)		Troponin (pg/ml)	NT- proBNP (pg/ml)	ECG
						E/MN	NE/NMN			
1	51/male	nausea, vomiting, dyspnea, palpitation	physical activity	no	left adrenal PHEO	5.9	2.5	1159	> 35000	sinus tachycardia, ST depression and T inversion in V ₄₋₆
2	38/male	nausea, vomiting, dyspnea, palpitation, headache	physical activity	no	bilateral adrenal PHEO	15.8	4.2	1220	5976	ST depression and T inversion in V ₁₋₆ , prolonged QTc interval
3	16/female	dyspnea	infection	no	right adrenal PHEO	normal	> 12.1	19.3	2985	sinus tachycardia
4	47/male	dyspnea, palpitation, sweating	no	yes	right adrenal PHEO	4.0	normal	2773	25492	sinus tachycardia, nonspecific T wave changes
5	49/female	dyspnea	no	no	left adrenal PHEO	11.2	11.9	77.3	4740	T wave inversion in inferior leads
6	62/male	dyspnea, palpitation, sweating	no	no	left adrenal PHEO	2.6	57.5	84.3	7976	diminished R wave in V ₂₋₃
7	51/male	dyspnea, chest pain	operation	no	right adrenal PHEO	-	-	130.2	2250	premature atrial complex
8	66/female	nausea, vomiting, dyspnea, sweating	defecation	yes	right adrenal PHEO	-	-	437.6	33914	T wave inversion in inferior leads and V ₂₋₆
9	29/male	nausea, dyspnea, palpitation, sweating	no	yes	left adrenal PHEO	8.4	11.4	663.6	26508	sinus tachycardia, second degree AVB
10	76/male	nausea, vomiting, dyspnea	no	no	right adrenal PHEO	9.4	2.9	2178	> 35000	sinus tachycardia, low voltage in limb leads, ST depression in V ₃₋₆
11	35/female	dyspnea, palpitation, sweating	pregnancy	yes	retroperitoneal PGL	-	-	-	-	T wave inversion in inferior leads and V ₃₋₆
12	46/male	nausea, vomiting, dyspnea, headache	no	yes	right adrenal PHEO	25.1	16.0	121.9	8946	T wave inversion in I, aVL, and V6

Case	Sex/age (years)	Initial symptoms	Triggers	Labile blood pressure	Location of tumors	Plasma catecholamine (× ULN)		Troponin (pg/ml)	NT- proBNP (pg/ml)	ECG
						E/MN	NE/NMN			
13	42/male	nausea, vomiting, dyspnea, chest pain, headache	no	no	left adrenal PHEO	10.4	7.6	954.2	12913	ST depression in inferior leads and V ₄₋₆ , ST elevation in aVR
14	52/male	dyspnea	no	no	pelvic PGL	normal	> 12.1	72.1	1208	sinus tachycardia, LBBB

Table 2
Characteristics of patients with ACCs (continued).

Case	Acute LVEF (%)	Strain analysis	Impaired patterns in LS	Acute global LS	Coronary artery evaluation	Recovery on imaging	Clinical diagnosis
1	0.38	yes	apical ballooning	-5.5	CTA: (-)	6 days	Takotsubo syndrome
2	0.39	yes	apical sparing	-10.7	CAG: (-)	7 days	Takotsubo syndrome
3	0.45	yes	apical sparing	-4.8	without risk factors	30 days	Takotsubo syndrome
4	0.21	yes	apical sparing	-6.1	without risk factors	14 days	Takotsubo syndrome
5	0.62	no	-	-	CAG: (-)	-	HFpEF
6	0.64	yes	apical sparing	-16.8	CTA: (-)	-	HFpEF
7	0.43	no	-	-	CTA: p-RCA 50% stenosis	12 days	Takotsubo syndrome
8	0.61	no	-	-	no	-	HFpEF, ischemic stroke
9	0.36	no	-	-	without risk factors	11 days	Recurrent Takotsubo syndrome (3 times)
10	0.38	yes	segmental	-21.2	CTA: (-)	11 days	Recurrent Takotsubo syndrome (2 times)
11	0.65	no	-	-	without risk factors	-	HFpEF
12	0.59	yes	apical sparing	-9.6	without risk factors	7 days	Takotsubo syndrome
13	0.35	yes	apical sparing	-13.6	CAG: (-)	15 days	Takotsubo syndrome
14	0.28	yes	global	-	CAG: (-)	without recovery in 10 months	Catecholamine-induced cardiomyopathy
Abbreviations: AVB: atrioventricular block; CAG: coronary artery angiography; CTA: coronary computed tomography angiography; E: epinephrine; HFpEF: heart failure with preserved ejection fraction; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; LS: longitudinal strain; LV: left ventricle; MN: metanephrine; NE: norepinephrine; NMN: normetanephrine; PGL: paraganglioma; PHEO: pheochromocytoma; p-RCA: proximal right coronary artery; ULN: upper limit of normal. Other abbreviations as shown in Table 1.							

In comparison to non-ACCs group, ACCs group shared similar characteristics in sex (male, 71.4% vs 45.1%, $P = 0.058$) and age (median, 48 vs 54, $P = 0.320$). As expected, more patients with ACCs had hypertension (78.6% vs 49.1%, $P = 0.034$); however, the patterns of hypertension didn't differ in two groups ($P = 0.266$). Surprisingly, the proportions of subjects who displayed classic triad symptoms (7.1% vs 8.6%, $P = 1.000$) and chest pain (14.3% vs 2.3%, $P = 0.065$) were similar and quite low among two groups; nevertheless, much more patients showed gastrointestinal symptoms (50.0% vs 6.3%, $P < 0.001$) and dyspnea (100% vs 8.0%, $P < 0.001$) in ACCs group. Expectedly, with regard to ECG changes, patients

with ACCs were more prevalent in both ST-segment changes (28.6% vs 8.9%, $P = 0.043$) and T wave inversions (50.0% vs 13.1%, $P = 0.002$) as compared to those without ACCs. In terms of laboratory findings, proteinuria was more likely to be prevalent in ACCs group (35.7% vs 11.1%, $P = 0.026$); likewise, ACCs group had higher median level of white blood cell (median, 15.6 vs 6.4, $P < 0.001$). Additionally, as for patterns of secretion, a combination of both dominated in patients with ACCs ($P = 0.044$); moreover, a higher prevalence of epinephrine-producing PPGLs (81.8% vs 33.9%, $P = 0.006$) was observed in ACCs group. Overall, the proportions of paragangliomas, bilateral adrenal tumors, and right adrenal tumors were similar between two groups; however, patients with ACCs exhibited a trend for having larger maximal tumor diameters, but the difference didn't reach statistical significance (median, 5.5 vs 4.5, $P = 0.053$). Interestingly, more patients in ACCs group showed invasive behavior (61.5% vs 27.3%, $P = 0.022$) and hemorrhage/necrosis (53.9% vs 17.4%, $P = 0.005$) on pathology report as compared with patients in non-ACCs group.

Strain analysis

As shown in Table 2, 2D strain analysis was carried out in 9 (64.3%) out of 14 patients with ACCs, and technical reasons accounted for the failure of analysis in the rest 5 cases. Strikingly, 6 (66.7%) patients displayed the pattern of relative apical sparing in LS; meanwhile, of the rest 3 patients, one (case 1) showed the pattern of apical ballooning, one (case 10) displayed the pattern of segmental dysfunction, and the last one (case 14) showed the pattern of global dysfunction. Of 7 patients with Takotsubo-like cardiomyopathy who underwent strain analysis, one patient (case 1) (14.3%) exhibited the typical apical ballooning pattern; however, 5 (71.4%) (case 2, 3, 4, 12, 13) cases showed the pattern of relative apical sparing in LS. Visual examples of patterns of 'apical ballooning', 'apical sparing', 'global' and 'segmental' in LS are depicted in Fig. 1 (panel A-G). Finally, the mean value of GLS was -11.0 ± 5.8 , with a range of -5.5 to -21.2.

Subclinical myocardial injuries

The prevalence of SMIs was potential to be underestimated owing to unthorough investigations or to be an overestimation because of the prescription of examinations being at discretion of physicians in this study. Only 74 (39.2%) patients had echocardiography examination, 55 (29.1%) received troponin test and 51 (27.0%) underwent NT-proBNP test; then, only 91 (48.2%) patients received at least one of the aforementioned three examinations. After excluding patients with ACCs, 21 (27.2%) cases out of 77 experienced SMIs, including elevated NT-proBNP in 15, elevated troponin in 4 and abnormal findings on echocardiography examinations in 10 patients (shown in Table 3).

Table 3
Characteristics of patients with SMIs.

Case	Sex/age (years)	Location of tumors	Blood catecholamine (× ULN)		Troponin (pg/ml)	NT-proBNP (pg/ml)	Echocardiography	Impaired patterns on strain analysis*
			E/MN	NE/NMN				
1	55/male	retroperitoneal PGL	normal	15.3	normal	normal	enlarged LA and LV, LVH	anterior and lateral segments
2	35/female	right adrenal PHEO	normal	33.1	-	-	LVH	apical sparing
3	31/male	retroperitoneal PGL	-	-	21.4	216.4	LVH	-
4	56/male	retroperitoneal PGL	normal	12.2	337.4	137.2	normal	normal
5	47/female	left adrenal PHEO	-	-	normal	350	enlarged LA	-
6	58/female	left adrenal PHEO	9.1	2.7	normal	366.6	normal	apical sparing
7	38/male	left adrenal PHEO	normal	> 12.1	normal	164.2	enlarged LA, LVH	anterior and lateral segments
8	65/male	retroperitoneal PGL	-	-	21	2140	-	-
9	70/male	left adrenal PHEO	4.9	4.8	-	-	normal	basal inferior segment
10	54/female	right adrenal PHEO	-	-	normal	153	normal	anterior and lateral segments
11	54/female	right adrenal PHEO	38.9	12.1	normal	778.4	LVH	-
12	67/female	left adrenal PHEO	normal	5.2	-	-	enlarged LA, LVH	anterior and lateral segments
13	31/male	left adrenal PHEO	normal	8.4	normal	303.8	-	-
14	39/female	left adrenal PHEO	7.6	9.9	normal	1008	normal	
15	67/male	right adrenal PHEO	2.8	7.4	-	-	segmental dysfunction, enlarged LA	anterior and lateral segments
16	56/female	right adrenal PHEO	4.0	1.9	normal	322.6	-	-
17	55/female	right adrenal PHEO	normal	normal	-	-	pulmonary hypertension	anterior segment
18	35/female	right adrenal PHEO	4.0	4.0	normal	408.5	-	-
19	23/male	right adrenal PHEO	normal	8.5	normal	337.7	-	-
20	57/female	right adrenal PHEO	normal	normal	48.39	215.8	-	-
21	40/female	left adrenal PHEO	-	-	normal	770	-	-
Abbreviations: LA: left atrium; LVH: left ventricular hypertrophy. Other abbreviations as shown in Tables 1 and 2.								
* not all patients with echocardiography examinations were suitable for two-dimension strain analysis.								

Discussion

In this retrospective study with a large sample size (189 cases), we demonstrated a relatively high prevalence (7.4%) of ACCs owing to catecholamine excess in patients with PPGLs. Moreover, 9 out of 14 patients with ACCs displayed Takotsubo-like cardiomyopathy, and 2D strain analysis further revealed that the predominant impaired pattern was apical sparing pattern (5/7), which dominated over the typical apical ballooning pattern seen in TTS (1/7). In fact, we believed that part of, if not all, patients diagnosed with HFpEF had gone through the clinical course of Takotsubo-like cardiomyopathy, since strain analysis showed impaired strain in case 6. Of note, SMIs had a fairly high incidence (27.2%) in patients who underwent cardiac biomarker examinations or echocardiography examinations, suggesting the universality of CAs-related cardiac injuries.

In this study, the majority (59.3%) of PPGLs were incidental findings on abdominal ultrasonogram or CT/MRI scan rather than PPGLs-related symptoms. The main discovery method is consistent with recent cohort studies, implying the changes in PPGLs recognition due to the widespread use of cross-sectional imaging; hence, the relatively low prevalence of hypertension and symptoms might be explained by the fact that most PPGLs were incidentally found in recent years[12, 13]. Nausea or vomiting occurred in half of the patients with ACCs, which should be partly, if not totally, ascribed to excessive CAs secretion[13]. The data was surprising to us given less than ten percent of patients showed classical triad symptoms, which was lower than the percent (17%) reported by recent study[13] and might be underestimated owing to the retrospective nature of the study. As with the strikingly low prevalence (4%) of classical triad in patients with PPGLs-induced reversible cardiomyopathy reported by recent review, the low rate in our study could help remind clinicians to consider PPGLs in the context of reversible cardiomyopathy with unclear etiology and not to rely on the classical triad as a diagnostic threshold[3].

Proteinuria was more prevalent in patients with ACCs as compared with non-ACCs controls, implying the more severe kidney injury brought by CAs or cytokines released from PPGLs[14]. Worth mentioning, epinephrine secretion was present in most cases (81.8%) with ACCs, which was consistent with previous studies[4], indicating episodic release of epinephrine causing sudden cardiac decompensation as opposed to persistent store and release for norepinephrine[15, 16]. A trend for larger tumor diameter was observed in ACCs-group compared to non-ACCs group ($P = 0.053$), and inconsistent correlations between tumor size and ACCs had been reported in prior studies[5–7]. Presence of hemorrhage/necrosis at histology was more often seen in subjects with ACCs than those without, suggesting the possible role as triggers played by hemorrhage/necrosis[2, 17]. In agreement with the recognition that all PPGLs have a metastatic risk, we reported a fairly high rate of invasive behavior on pathology report (29.7%). Additionally, invasive behavior seemed to be associated with ACCs; however, the result should be considered exploratory owing to the lack of standardization of interpretation of pathology results and well-accepted histological features indicating metastasis[18].

The prevalence (4.8%) of Takotsubo-like cardiomyopathy in our cohort was comparable with the 1.4 ~ 5.6% prevalence reported in previous studies[4–8]. The apical sparing pattern (5/7), indicating mid-ventricular and/or basal impairment, dominated in the impaired patterns of LS whereas prior reviews revealed a predominance (48%) of classical apical ballooning pattern on routine echocardiography examinations[3, 4]. The different impaired patterns between PPGLs-induced TTS and classic TTS hint that distinct pathogenetic mechanisms may exist among them[19, 20]. Recurrent TTS associated with PPGLs were reported and systematically reviewed by our team recently[21]; note, two patients experienced recurrent episodes of TTS and were diagnosed as myocarditis in 2 ~ 4 years before identifying PPGLs in this cohort, highlighting the value of screening for the presence of PPGLs among these patients.

Unexpectedly, a quite high prevalence (27.2%) of SMIs in patients with PPGLs was observed in our study, implying that cardiac injury without clinical manifestations is common in the presence of excessive CAs release. The abnormalities in ECG examinations, including sinus tachycardia, atrial fibrillation, premature complex, and nonspecific ST-T changes, were not deemed as SMIs because they were unspecific for PPGLs-related cardiac injuries; hence, the occurrence rate of SMIs might be underestimated.

Strengthens and limitations of this study

This study is a first study aimed to investigate the PPGLs-induced ACCs and SMIs in East-Asian population with a large sample size. It is the first time to characterize the echocardiography abnormalities on strain analysis and demonstrate that the primary pattern was apical sparing pattern. In addition, the high prevalence, possibly being underestimated, of SMIs observed in this study were not reported in previous cohort studies. However, limitations are obvious, including the followings: firstly, we were not able to perform comprehensive assessments of the cardiac injuries attributed to tremendous amount of CAs because of the retrospective nature of the study; secondly, due to lack of genetic screening, the diagnoses made in this cohort failed to meet the requirement in current guidelines[10]; thirdly, the low number of events made it impossible to conduct regression analyses to reveal the independent factors associated with ACCs; finally, it should be cautious to expand the results owing to center-specific referral bias.

Conclusion

Collectively, this study with retrospective design revealed that one in every fourteen PPGLs patients presented with ACCs. The main impaired pattern in patients with TTS on strain analysis was apical sparing pattern, which is distinct from previous studies. Moreover, nearly one-third of patients without symptoms had SMIs. Clinical clues suggestive of PPGLs should not rely solely on adrenergic symptoms, particularly classic triad, due to its extremely low prevalence. Clinicians should consider PPGLs in patients with acute reversible cardiomyopathy, especially with an apical sparing pattern in LS.

Abbreviations

ACCs: acute cardiac complications; CAG: coronary artery angiography; CAs: catecholamines; CT: computed tomography; CTA: coronary computed tomography angiography; ECG: electrocardiography; eGFR: estimated glomerular filtration rate; GLS: global longitudinal strain; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; LS: longitudinal strain; MN: metanephrine; MNs: metanephrine / normetanephrine; MRI: magnetic resonance imaging; NMN: normetanephrine; NT-proBNP: N-terminal pro-B type natriuretic peptide. PGLs: paragangliomas; PHEOs: pheochromocytomas; PPGLs: pheochromocytomas and paragangliomas; SD: standard deviation; SMIs: subclinical myocardial injuries; TTS: Takotsubo syndrome; ULN: upper limit of normal.

Declarations

Ethics approval and consent to participate

All patient records were anonymized before analysis and the requirement for informed consent was waived by the Institutional Review Boards (IRB) due to the retrospective nature of the study. The study protocol was approved by the IRB of Soochow University and followed the principles of the Helsinki Declaration.

Consent for publication

Not applicable.

Availability of data and material

The data used for analysis can be available by corresponding author per reasonable request.

Competing interests

The author declare that they have no competing interests.

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Authors' contributions

Y-L D designed this study. JZ, J-T H and HX made substantial contributions to acquisition of the data. Y-L D, JZ and HX were involved in data analysis. 2D strain analysis was performed by Y-X M. Y-L D, JZ and HX wrote the manuscript. All author approved the final version of the manuscript.

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Figures

Figure 1

Representative impaired patterns in longitudinal strain for each subgroup. (A) The pattern of apical ballooning in case 1. (B) The pattern of segmental dysfunction in case 10. (C) The pattern of global dysfunction in case 14. (D-F) The patterns of apical sparing in case 2, 6, and 12. (G1, 2) The apical sparing pattern in acute phase and a nearly full recovery 14 days later in case 4.