CASE REPORT

Anesthetic Management of Clinically Silent Familial Pheochromocytoma with MEN 2A: A Report of Four Cases

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Abstract Familial pheochromocytomas are commonly associated with multiple endocrine neoplasia type 2 (MEN 2) syndrome. Majority of the patients present with normal clinical and biochemical parameters in the preoperative period, the incidence of hypertension being only 50 %. Even though patients may be clinically asymptomatic, surveillance and proper preoperative evaluation is important, as surgery for associated tumors may precipitate a hypertensive crisis and result in severe complications. A family of 19 members, of which 12 were positive for MEN 2A syndrome, presented to our hospital. Seven of the 12 patients had pheochromocytoma and medullary thyroid carcinoma (MTC), while the other 5 had only raised plasma calcitonin levels. Two of the 7 patients presented with bilateral pheochromocytoma and underwent an open adrenalectomy. The other 5 patients had a left-sided adrenal tumor and underwent left laparoscopic adrenalectomy under combined general and epidural anesthesia. We present our experience with four of these five cases. We here state that how paucity of literature on perioperative preparation of clinically and biochemically silent pheochromocytomas led to serious intraoperative complications in one of four cases.

Keywords Familial pheochromocytoma · MEN · Multiple endocrine neoplasia · Plasma metanephrines · VMA · Vanillylmandelic acid

Introduction

Clinically silent pheochromocytomas are usually detected on routine screening of patients in families with autosomal dominant inherited disorders like multiple endocrine neoplasia type 2 (MEN 2), von-Hippel-Lindau disease, and neurofibromatosis type 1 [1–3]. Such patients are radiologically and genetically positive but maybe biochemically negative (plasma/urinary metanephrines, vanillylmandelic acid (VMA), and catecholamines) on routine screening.

We present here the anesthetic management of four patients of a family with MEN 2A series, all of whom were asymptomatic and only two were biochemically positive. All the patients were however radiologically and genetically positive for pheochromocytoma.

Although the anesthetic management of clinically active pheochromocytomas is clearly defined [4], there are no clear guidelines on the management of silent pheochromocytomas especially those that are biochemically negative. We wish to highlight how lack of consensus guidelines especially regarding perioperative preparation of biochemically silent pheochromocytomas led to a major intraoperative life-threatening anesthetic complication in one of the patients.

Case Presentation

Twelve members out of a family of 19 presented to our hospital with MEN 2A syndrome. Of these 12 patients, 7 had both pheochromocytoma and MTC while 5 had only raised plasma

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Table 1 Preoperative case summary

Case	Age/sex	Biochemical profile	Imaging (CT scan)	Symptoms	Genetic mutation (RET proto-oncogene)
Case 1	22/M	Normal urinary VMA and catecholamines	4 × 2 cm left adrenal mass	Nil	Positive
Case 2	28/M	Normal urinary VMA and catecholamines	1 × 4 cm left adrenal mass	Nil	Positive
Case 3	24/F	↑Plasma metanephrines, normal urinary VMA and catecholamines	5 × 3 cm left adrenal mass	Nil	Positive
Case 4	21/F	↑Urinary metanephrines, ↑urinary catecholamines	3 × 2 cm left adrenal mass	Nil	Positive

↑ = increased; VMA vanillylmandelic acid, CT computed tomography

calcitonin levels. The remaining 5 patients had unilateral disease, and a left laparoscopic adrenalectomy was performed on them. We present the perioperative preparation and management of four of these five cases (Table 1).

Case 1

The patient was clinically asymptomatic and had a normal biochemical profile with respect to urinary VMA and plasma catecholamines. Due to a lack of availability in our setup and cost constraints, metanephrine levels could not be done. As there were no clear guidelines for preoperative preparation of biochemically negative cases, we decided to take up the patient without pharmacological preparation. The patient was posted for laparoscopic adrenalectomy under general anesthesia (GA) supplemented with epidural. Central venous pressure (CVP) and invasive arterial pressure (IBP) monitoring was done. On tumor handling, the patient developed tachycardia (heart rate ranging from 100 to 180 bpm), hypertension (mean arterial pressure ranging from 120 to 180 mmHg), and cardiac dysrhythmias (supraventricular tachycardia and ventricular tachycardia) (Fig. 1). Despite timely management with

antihypertensives and antiarrhythmics (nitroglycerin, sodium nitroprusside, phentolamine, esmolol, xylocard, and amiodarone), the patient developed pulmonary edema on adrenal vein clipping and had to be shifted to the intensive care unit (ICU), where he stayed for 7 days before recovery.

Case 2

The second patient was also asymptomatic and biochemically negative (VMA and urinary catecholamines). Due to constraints, metanephrine levels could not be done, but having learnt from the first case, we decided to prepare the patient preoperatively with alpha- and beta-blockers.

Cases 3 and 4

Both the patients were clinically asymptomatic but had raised metanephrine levels (plasma and urine, respectively). Majority of literature supports preoperative preparation with alpha- and beta-blockers in all metanephrine-positive familial pheochromocytomas [5, 6].

Fig. 1 Intraoperative hemodynamic fluctuations in case 1. *SBP* systolic blood pressure (mmHg), *DBP* diastolic blood pressure (mmHg), *HR* heart rate (beats/minute)

Patients 2, 3, and 4 were prepared with an alpha-blocker (prazosin 2.5 mg tab HS) for 2 weeks preoperatively, and a beta-blocker (atenolol 25 mg tab OD) was added 1 week prior to surgery. The end point of Roizen criteria (no orthostatic hypotension with BP $\leq$ 80/45 mmHg and no ST-T wave changes) was achieved in 2 weeks [5]. Alpha- and beta-blockers were continued till the day of surgery. All the patients remained hemodynamically stable in the intraoperative period and required minimal doses of vasodilator and inotropic agents. They were extubated smoothly in the operation theater and sent to the ICU for observation for 1 day.

Discussion

Patients with familial pheochromocytoma are usually clinically silent and rarely present with the classic triad of headache, palpitations, and sweating [2]. Paroxysmal release of epinephrine with continuous metabolism results in low or undetectable plasma and urinary catecholamines [1, 2]. Twenty-four-hour urinary-free catecholamines which are confirmatory for a diagnosis of symptomatic pheochromocytomas cannot be relied upon, and plasma/urine metanephrines are considered the diagnostic marker for clinically silent pheochromocytomas [3].

Routine screening of family members diagnosed with MEN 2A should be carried out to detect silent pheochromocytomas, as patients may land up with severe perioperative hypertensive crisis in the case of an incidental or emergency surgery. Family members are screened on the basis of genetic markers and computed tomography of the abdomen for detection of the adrenal mass. Annual determination of plasma-free metanephrines has been recommended as it is the most sensitive marker for the diagnosis of familial pheochromocytomas [2, 3]. Our cases, too, were screened by biochemical, radiological, and genetic markers.

There is a paucity of literature on the preoperative preparation of clinically and biochemically silent pheochromocytomas [6–8]. Our first patient developed pulmonary edema following clamping of the adrenal vein, due to a sudden surge of catecholamines. In view of this experience and the fact that metanephrine levels could not be done in cases 1 and 2, we decided to prepare the case preoperatively with alpha- and beta-blockers, which ultimately resulted in an uneventful perioperative course.

Kumar et al. reported a similar experience in a 30-year-old male patient whose biochemical profile including plasma metanephrine levels was within normal range. The patient was not prepared preoperatively, and during resection of the pheochromocytoma, he developed a severe hypertensive crisis, due to which surgery was postponed. The patient was taken up after 2 weeks of pharmacological optimization and thereafter had an uneventful perioperative course [7].

In contrast, Trivedi et al. reported an uneventful perioperative course of a familial biochemically silent pheochromocytoma (with normal metanephrine levels) without preoperative pharmacological optimization [8]. Such conflicting case reports about the anesthetic management of clinically silent pheochromocytomas have been reported by many other authors [9, 10].

There is more clarity regarding the anesthetic management of clinically silent and biochemically positive pheochromocytomas. Such patients should be adequately prepared with alpha-blockers (using Roizen criteria) and beta-blockers preoperatively [5, 9, 10]. Therefore, we prepared cases 3 and 4 who were biochemically positive but clinically asymptomatic as per these recommendations.

Although there is paucity of literature regarding preoperative optimization of biochemically silent pheochromocytomas, we recommend that all such patients be optimized preoperatively with adrenergic blockers and intraoperative precautions taken, including hemodynamic monitoring, to ensure a stable perioperative course. This is especially important in patients where screening for plasma and urinary metanephrines is either not available or not feasible.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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