Pituitary apoplexy after cardiac surgery in a 14-year-old girl with Carney complex: a case report

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Abstract. A 14-year-old girl was referred to our department because of headache and visual impairment following the resection of recurrent cardiac myxoma. Head magnetic resonance imaging (MRI) scan detected an intra- and supra-sellar tumor. Moreover, the patient showed the presence of spotty skin pigmentation on her cheeks and lower lip. Blood examination revealed hypothyrotropinemia, and ultrasonography results revealed multiple thyroid nodules. She was diagnosed with Carney complex (CNC). Her pituitary tumor was suspected as growth hormone (GH)-secreting adenoma, because overgrowth was observed in the patient. However, biochemical examinations, including oral glucose tolerance test, failed to show the characteristic findings of GH-secreting adenoma. In contrast, insulin tolerance test showed GH deficiency. Her visual impairment improved without performing decompression surgery, and the tumor size decreased, as per the MRI findings. Based on clinical course, the patient was diagnosed with pituitary apoplexy in pituitary adenoma, following which she was discharged. At 3 months after discharge, thyrotropin-releasing hormone loading test performed revealed low thyrotropin-stimulating hormone and thyroid hormone levels, and the patient was in a depressed mood. Therefore, I-T4 replacement was initiated, following which her GH secretory capacity gradually improved. Here, we report, to the best of our knowledge, the first case of a patient with pituitary apoplexy in CNC. Such condition must be identified in young patients with recurrent cardiac myxoma, and examinations, such as head MRI, must be performed.

Key words: Pituitary apoplexy, Carney complex, Pituitary tumor, Cardiac myxoma

PITUITARY APOPLEXY is a rare disease with an annual incidence of 0.17 episodes per 100,000 in all generations [1]. Pituitary apoplexy in children and adolescents is extremely rare, as pituitary tumors are rare in those age group. The primary cause of pituitary apoplexy is an underlying pituitary tumor, particularly a nonfunctioning adenoma in adults and a functioning adenoma in children and adolescents [2]. In symptomatic cases, main symptoms are headache, visual impairment, vomiting, ophthalmoplegia, and altered level of consciousness.

Carney complex (CNC) is a clinical syndrome characterized by cardiac and other myxoma, spotty skin pigmentation, and endocrine tumors, such as growth hormone (GH)-secreting adenoma. The mutation in protein kinase A regulatory subunit 1 alpha (\textit{PRKAR1a}) causes CNC, although not all patients with CNC carry the mutation [3].

Herein, we report the case of a patient with CNC that was diagnosed because of the presence of pituitary apoplexy following the resection of recurrent cardiac myxoma.

Case Report

A 14-year-old girl had a resection of cardiac myxoma in the right ventricle at the age of 12 years. Overall, she was healthy and did not have any family history of diseases. Her puberty started just before 8 years, but her menarche had not initiated before surgery. Recurrent cardiac myxoma in the right ventricle was observed during a follow-up examination. She successfully underwent a resection surgery using extracorporeal circulation. The day after surgery, she complained of headache and visual impairment, and her menarche started on that day. A few days after surgery, she had a vaginal bleeding. On the seventh day after surgery, she underwent head computed
tomography (CT) scan, and results revealed a tumor surrounding the hypothalamic–pituitary lesion. She was referred to our department for further evaluation.

The patient’s weight and height were 173.2 cm (+3.2 standard deviation (SD)) and 63.5 kg (+1.7 SD), respectively (Fig. 1A). Her target height is 159.5 cm, as her father’s height and mother’s height are 172 cm and 160 cm, respectively. Her body temperature, blood pressure, and pulse rate were 36.7°C, 120/80 mmHg, and 80 beats per minute, respectively. Her Glasgow coma scale score was 15. Edema and goiter were not observed. Tanner stage was B3 and bone age was 12.5 years (TW2-RUS). However, the patient showed the presence of spotty skin pigmentation on her cheek and lower lip (Fig. 1B).

Blood examination showed hypothyrotropinemia (thyrotropin-stimulating hormone (TSH)) level was 0.103 μIU/mL, FT4 level was 0.87 ng/dL, and FT3 level was 2.28 pg/mL); moreover, elevated HbA1c (NGSP) (6.2%) was observed (Table 1). Head magnetic resonance imaging (MRI) scan showed an intra- and suprasellar tumor with a maximal diameter of approximately 30 mm. The tumor revealed heterogeneous signal intensity on T2 weighted (T2W) coronal image (Fig. 2A) and slightly high intensity on T1 weighted (T1W) coronal image (Fig. 2B). Optic chiasma and bilateral optic nerves were compressed by the tumor on heavy T2W coronal image (Fig. 2C). On post-gadolinium contrast T1W coronal image, enhancement was seen at the peripheral and partially inside of the mass (Fig. 2D). The tumor invaded into the left cavernous sinus (Fig. 2D). Mucosal thickening in the sphenoid sinus was also identified (Fig. 2A and D). Thus, we could consider the pathophysiology of pituitary apoplexy in the present case is due to the hemorrhagic infarction. She had declined visual acuity without ophthalmoplegia, and visual field defect of both eyes (Fig. 2F). Echographic examinations revealed the presence of multiple thyroid nodules (Fig. 2G). Abdominal CT scan revealed the absence of primary pigmented nodular adrenocortical disease (PPNAD). The patient was then diagnosed with CNC according to the diagnostic criteria of this disease. We considered her pituitary tumor as GH-secreting adenoma because acromegaly due to GH-secreting adenoma is one of the characteristic features of CNC; moreover, her growth chart showed overgrowth, which can be attributed to acromegaly. However, her IGF-1 levels were within the reference range for her age (Table 1), and 75-g oral glucose tolerance test (OGTT) results showed low GH levels at baseline and suppressed GH levels (<1.0 ng/mL) (Fig. 3A). To evaluate pituitary function, we performed thyrotropin-
releasing hormone (TRH) loading test and insulin tolerance test (ITT); results of these tests showed low response of TSH, no increase of GH but preserved hypophysial-adrenocortical secretory capacity in response to hypoglycemia (nadir blood glucose levels was 45 mg/dL) (Fig. 3B and C). Urgent surgical decompression was considered, as she showed the presence of visual impairment, which could be attributed to optic chiasmal compression. However, conservative treatment was chosen as an alternative management because her visual impairment improved (Fig. 2H). Steroid replacement therapy was not initiated, as her vital sign was stable and biochemical tests including electrolytes and 24 h excretion of urinary free cortisol level were within normal range. On the 21st day after cardiac surgery, follow-up MRI was performed and revealed that the tumor size decreased with optic nerves decompression and the thickening of sphinoid mucosa also disappeared (Fig. 2E). Based on clinical course, the patient was diagnosed with pituitary apoplexy in pituitary adenoma. The patient was discharged on the 23rd day after surgery.

Three months later, we re-evaluated her pituitary function via triple loading test (insulin, TRH and LHRH) (Table 2) and GHRP2 loading. TRH loading test results showed low response of TSH with low levels of thyroid hormones (FT4 level at 0 min was 1.11 ng/dL) (Fig. 3D). ACTH and cortisol responses to hypoglycemia were slightly decreased (Fig. 3E). GHRP2 loading test showed low response of GH levels (peak GH 7.91 ng/mL) (Fig. 3F). Basal GH levels were around 2 ng/mL and showed markedly diminished responses to hypoglycemia. She was in a depressed mood and was absent from school. She began l-T4 treatment. At 3 months after the initiation of l-T4, GHRP2 loading test was again performed. The peak in GH levels was 9.35 ng/mL, which showed a higher peak level compared to the previous loading test. Thirteen months later, her menstruation resumed. After eighteen months, we re-performed triple loading test (Table 2). The results at 18 months after cardiac surgery were almost same as the results performed at 3 months after cardiac surgery. IGF-1 levels decreased to the levels under –2 standard deviation (166 ng/mL) and HbA1c

| Table 1  | Laboratory findings |
|----------|---------------------|
| Haematology | Biochemistry | Endocrine |
| WBC | 9,500 μL | TP | 8.4 g/dL | TSH | 0.103 uIU/mL (0.35–4.9) |
| Neutro | 67 % | Alb | 4.3 g/dL | FT3 | 2.28 pg/mL (1.7–3.7) |
| Eosino | 4 % | LDH | 328 U/L | FT4 | 0.87 ng/dL (0.7–1.48) |
| Lymph | 25 % | AST | 17 U/L | LH | 1.05 mIU/mL (1.1–12.1) |
| Hb | 11.9 g/dL | ALT | 18 U/L | ACTH | 15.5 μg/mL (7.2–63.3) |
| RBC | 4.65 × 10^12/L | ALP | 463 U/L | PRL | <0.1 ng/mL (0–0.1) |
| Plt | 455 × 10^3 μL | BUN | 21.9 mg/dL | βhCG | 103 mmol/L |
| Hct | 38.3 % | Cre | 0.72 mg/dL | Na | 144 mmol/L |
| Plt | 455 × 10^3 μL | UA | 8.3 mg/dL | K | 4.2 mmol/L |
| Cl | 103 mmol/L | T-cho | 156 mg/dL | Mg | 109 mg/dL |
| CK | 107 U/L | BS | 97 mg/dL | |
| HbA1c | 6.2 % | |

WBC, white blood cell; Neutro, neutrophil; Eosino, eosinophil; Hb, hemoglobin; RBC, red blood cell; Hct, hematocrit; Plt, platelets; TP, total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cre, creatinine; Na, sodium; K, potassium; Cl, chloride; T-cho, total cholesterol; TG, triacylglyceride; CK, creatin kinase; BS, blood sugar; TSH, thyroid-stimulating hormone; FT3, free tri-iodotyronine; FT4, free thyroxine; IGF-1, insulin-like growth factor-1; LH, luteinizing hormone; FSH, follicle-stimulating hormone; E2, estradiol; ACTH, adrenocorticotropic hormone; PRL, prolactin; βhCG, human chorionic gonadotropin; Normal ranges are shown in parentheses.
levels went down to the normal range (5.5%). Genetic examination by using blood cells showed no mutation in PRKAR1A gene. Informed consent was obtained from the patient and her parents for publication of this case report and accompanying images.

Discussion

Pituitary apoplexy is extremely rare in children and adolescents. However, the study investigating intratumoral hemorrhage in patients with pituitary adenoma by MRI and operative findings has reported the incidences of intratumoral hemorrhage in pituitary adenoma are 42.9% in childhood and 17.2% in adults, suggesting that younger patients have high risk of intratumoral hemorrhage compared to adult patients [2]. In the present study, MRI images clearly shows the pituitary apoplexy due to pituitary adenoma infarction. The thickening of sphenoid sinus mucosa is specific to the acute stage of pituitary apoplexy [4]. The mechanism of the sphenoid sinus mucosa might be venous congestion due to obstruction of intrasellar venous flow caused by the increment of intrasellar pressure. The thickening of sphenoid sinus mucosa is reported to disappear one week after the onset of apoplexy. In fact, follow-up MRI performed 2 weeks after the onset did not show the thickening of sphenoid sinus mucosa in the present case. Some precipitating factors of pituitary apoplexy have been suggested as follows; (i) alteration in blood flow in the pituitary gland (both reduced and acute increase in blood flow), (ii) an anticoagulant state, (iii) stimulating the pituitary gland. In the present study, the patient underwent cardiac surgery for cardiac myxoma, and anticoagulant was administered during surgery. Hemodynamic instability during cardiac surgery and use of anticoagulant might have caused pituitary apoplexy. The inherent features of pituitary tumor might be involved in the onset of pituitary apoplexy. Pituitary tumors have a high-energy demand but have poor blood supply because of the low expression of angiogenic factors and limited blood supply. The imbalance between tumor perfusion...
Fig. 3 Results of the hormone loading test. A. Oral glucose tolerance test. B. TRH loading test. C. Insulin tolerance test. D. TRH loading test 3 months after surgery. E. Insulin tolerance test (red line, plasma ACTH; green line, serum cortisol). F. GHRP2 loading test.

Table 2 Results of pituitary function at 3 month and 18 month after cardiac surgery (triple tests using Insulin, TRH and LHRH)

| min  | GH (ng/mL) | ACTH (pg/mL) | cortisol (μg/dL) | LH (mIU/mL) | FSH (mIU/mL) |
|------|------------|---------------|------------------|-------------|--------------|
| 3m   | 0          | 2.00          | 13.6             | 6.4         | 3.50         | 6.56        |
|      | 30         | 2.63          | 19.2             | 7.6         | 8.17         | 6.70        |
|      | 60         | 2.52          | 15.3             | 9.1         | 7.55         | 7.14        |
|      | 90         | 2.25          | 12.8             | 7.6         | 5.92         | 7.40        |
|      | 120        | 2.25          | 12.0             | 6.8         | 5.82         | 7.16        |
| 18m  | 0          | 2.01          | 16.5             | 7.7         | 5.35         | 6.15        |
|      | 30         | 2.89          | 28.2             | 9.9         | 12.87        | 7.94        |
|      | 60         | 2.61          | 19.4             | 9.2         | 10.86        | 7.64        |
|      | 90         | 2.18          | 13.8             | 7.2         | 8.78         | 7.75        |
|      | 120        | 2.11          | 13.0             | 6.5         | 8.26         | 7.76        |

GH, growth hormone; ACTH, adrenocorticotropic hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone
and metabolism may cause an acute ischemia or infarction [5, 6]. The major cause of the difference in the incidence between children and adults might be physiological enlargement of pituitary. Pituitary gradually enlarges during childhood and adolescents [7, 8]. It is possible that this physiological enlargement of pituitary is a chronic stimulating factor causing intratumoral hemorrhage in younger patients with adenoma.

The patient was diagnosed with CNC according to the diagnostic criteria of such condition [9]. Her pituitary tumor was considered as GH-secreting adenoma because of the diagnosis of CNC and overgrowth based on her growth chart. However, examinations result, including that of OGTT, did not indicate active acromegaly. ITT and GHRP-2 showed diminished increase in GH, indicating GH deficiency. Curiously basal GH levels were maintained. Hemorrhage in the pituitary gland might have caused necrosis and compression of GH-producing cells, causing deficiency in GH secretion. Urgent surgical decompression was considered, as she showed the presence of visual impairment, which could be attributed to optic chiasmal compression. However, conservative treatment was chosen as an alternative management because her visual impairment tended to improve. In UK, the scoring system named as the pituitary apoplexy score is used to assess whether patients could be managed conservatively [10]. Patients aged below 20 years with cardiac myxoma and/or those with cardiac myxoma localized in the right chamber are at high risk of CNC. Her growth chart indicated that her height is much higher than her target height, which is likely due to excessive GH secretion. One of the common features in patients with CNC is acromegaly, which is caused by GH-secreting adenoma or GH hypersecretion of the pituitary gland surrounding non-GH-secreting adenoma [11]. Most patients with pituitary apoplexy have poor hormonal outcomes and persistent hormonal deficiencies [12]. In the present study, the patient presented with multiple hormone deficiencies (TSH, gonadotropin, and GH) following the development of pituitary apoplexy. It is reported that surgical decompression could bring good hormonal consequence in children [13], thus we should have chosen surgical decompression in the present case. However, pituitary deficiencies gradually improved. Pituitary function after apoplexy does not usually recover completely without the need of hormone replacement. On the contrary, hormone-producing adenoma showed persistent or recurrent endocrine overactivation following the development of pituitary apoplexy [14]. Thus, her hormonal condition must be cautiously followed-up.

CNC was first described in 1985, and it is a clinical syndrome characterized by cardiac and other myxoma, spotty skin pigmentation, and endocrine tumors [15]. One of its most specific manifestations is PPNAD. Approximately 45%-65% of CNC families have heterozygous inactivating mutations in PRKAR1A [16, 17]. Patients with PRKAR1A are more likely to have PPNAD. Mutation analysis using peripheral blood cells in the present study showed no mutation in PRKAR1A. However, we can not completely exclude mutation in PRKAR1A, as we have not performed mutation analysis using the tissue of cardiac myxoma. Stratakis et al. have reported that 2p16 is also involved in the etiology of CNC [18]. Further genetic examination should be performed in the present study.

The present study showed the occurrence of pituitary apoplexy in a 14-year old girl with CNC. To the best of our knowledge, this is the first case of CNC complicated with pituitary apoplexy. CNC must be identified when assessing patients with recurrent cardiac myxoma.

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Disclosure

The authors declare no conflicts of interest.

Author Contributions

Y.N., J.M., A.T., S.Y., H.N., T.I., K.T., and H.H. attended to the patient; Y.N., J.T. and J.M. wrote the manuscript; Y.N., J.M., J.T., H.N., T.M., and H.H. gave conceptual advice. All authors have read and approved the final manuscript.

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