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Cardiac anesthesia in idiopathic hypereosinophilic syndrome

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Introduction

Idiopathic hypereosinophilic syndrome (IHS) is a rare clinical condition in which persistent eosinophilia of an unknown etiology is associated with multiple organ system dysfunctions [1–3]. The extent of organ system dysfunction is variable, ranging from minor skin lesions to serious cardiovascular and neurological dysfunctions. Cardiac manifestation includes endocardial fibrosis, restrictive cardiomyopathy, and valvular dysfunction, and is the major cause of morbidity and mortality [4]. Valve involvement commonly results in atrioventricular regurgitation, and valve replacement in IHS is appropriate if extracardiac manifestation of the eosinophilic process are controlled [5]. This case report describes a patient with IHS who underwent mitral valve replacement and tricuspid annuloplasty for mitral and tricuspid regurgitation, while also discussing anesthetic considerations for cardiac surgery in a patient with this syndrome.

Case report

A 25-year-old man, in whom IHS was diagnosed 13 months earlier, was admitted to our hospital complaining of general fatigue, dyspnea, and abdominal distention. When diagnosed, it was recognized that, in relation to IHS, he had endocardial fibrosis with restriced diastolic inflow, intracavitary thrombosis with decreased left ventricular (LV) cavity size, mitral regurgitation (MR) due to mitral valve (MV) prolapse, hepatosplenomegaly, and branch retinal artery occlusion of the right fundus. He had been treated with steroid (prednisolone [PNL]; max. 60 mg·day^{-1}) and warfarin for the control of eosinophilia and for the thrombosis, respectively, but the therapy was discontinued 5 months prior to admission after achieving satisfactory control of the eosinophilia. On admission, he appeared chronically ill. A holosystolic murmur (Levine III/VI) and a third sound was audible at the apex. His abdomen was distended and liver edge was palpable 4 finger-breadths (FB) below the costal margin. His lower extremities were slightly edematous. The remainder of the examination was unremarkable. Laboratory investigations revealed: hemoglobin 11.4 g·dl^{-1}, WBC 7.7 × 10^9 liter^{-1} (49% eosinophils, 37% lymphocytes, 13% neutrophils, 1% monocytes), platelets 119 × 10^9 liter^{-1}; total bilirubin 1.4 mg·dl^{-1}, with direct bilirubin 0.7 mg·dl^{-1}, alkaline transferase 408 IU liter^{-1}; IgE 33 IU ml^{-1}. The patient's serum concentrations of protein, transaminase, urea, creatinine, and electrolytes were all normal. The chest radiograph revealed an enlarged heart (cardiothoracic ratio, 58.6%) with increased pulmonary vascularity. Ultrasonography showed a large MR due to MV prolapse, moderate to large tricuspid regurgitation (TR), mild pulmonary hypertension (PH), mild LV dysfunction (ejection fraction, 62%), moderate hepatosplenomegaly and mild ascites. Cardiac catheterization also showed large MR, mild PH (45/29 mmHg) and mild LV dysfunction (cardiac index, 2.24 L·min^{-1}·m^2). Monofocal ventricular premature captures were sporadically observed on ambulatory electrocardiogram recordings. Thereafter, extensive investigations for parasitic infection, allergic disorders, and other conditions associated with eosinophilia all proved to be negative, which supported the previous diagnosis. Consequently, severe

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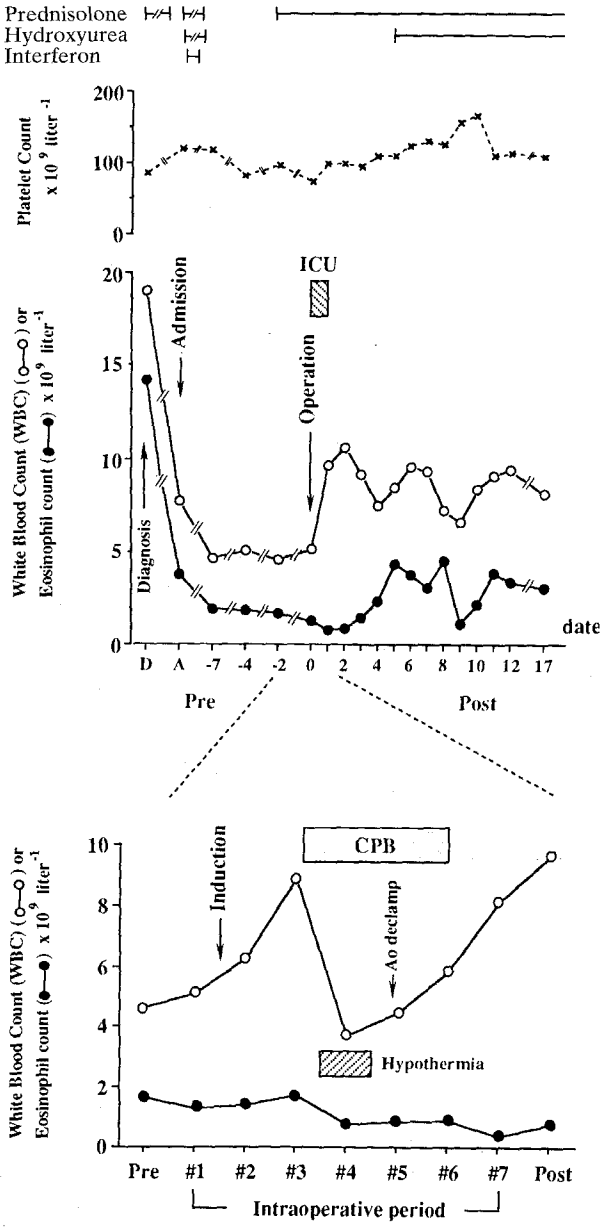

Fig. 1. The effects of therapy, general anesthesia, cardiac surgery, cardiopulmonary bypass and hypothermia on white blood cell count (*open circles*) eosinophil count (*closed circles*), and platelet count (*X*) in a patient with idiopathic hypereosinophilic syndrome (IHS) who underwent mitral valve replacement and tricuspid annuloplasty. Zero on the x-axis indicates the date when the operation was performed. Intraoperatively, blood was sampled before the induction of anesthesia (#1), just after the induction (#2), just before initiation of the cardiopulmonary bypass (*CPB*) or hypothermia (#3), during the CPB or hypothermia (28.7°C) (#4), just after the declamping of the aorta (#5), just after the end of the CPB (#6), and at the end of the operation (#7). No significant increase in eosinophil count was observed intraoperatively. Note that medication with prednisolone was started 2 days before the operation to prevent an increase in the eosinophil count during the perioperative period. *D*, date when IHS was diagnosed; *A*, admission date; *Pre*, preoperative date; *Post*, postoperative date; *ICU*, intensive care unit

chronic heart failure (NYHA class III) due to large MR associated with IHS was diagnosed.

Although his eosinophilia had been moderately improved by treatment with steroid (PNL), hydroxyurea (HU), and interferon (IFN) for about 8 months after the admission, the patient's cardiac condition did not improve despite treatment with digitalis, diuretics, and vasodilators, probably due to severe MR. Finally, mitral valve replacement and tricuspidal annuloplasty were planned. Although the above medication for the eosinophilia was discontinued for about 1 month prior to surgery because of satisfactory control of the eosinophilia, he was administered PNL for 2 days before the surgery to prevent an increase in the eosinophil counts during the perioperative period (Fig. 1). He was premedicated with nitrazepam 8 mg and prednisolone 10 mg orally 1.5 h before surgery. After a few minutes preoxygenation, anesthesia was induced with diazepam 10 mg and fentanyl 20 $\mu g \cdot kg^{-1}$, and his trachea was intubated after the administration of pancuronium 6 mg. Anesthesia was then maintained with air, oxygen, fentanyl 70 $\mu g \cdot kg^{-1}$, diazepam 2.5 mg, and pancuronium. Intraoperatively, he was monitored using an oxygen analyzer, pulse oximeter, capnometer, ECG, EEG, a radial artery catheter, a pulmonary artery catheter with mixed venous oximetry, a left atrial catheter (after cardiopulmonary bypass), rectal, esophageal and skin temperature probes and a urine catheter. Arterial blood sampling was performed to analyze blood gas, acid-base, electrolytes, and hematological status, where necessary. The pre-bypass period was uneventful, and there was no need to use any vaso- or cardioactive drugs. Methylprednisolone (M-PNL, 1240 mg) was administered intravenously before the initiation of a cardiopulmonary bypass (CPB). The CPB was initiated smoothly as usual. Intraoperative findings were consistent with the preoperative diagnosis. The posterior MV leaflet was generally thickened, extremely shortened, and almost immovable. The anterior MV leaflet was also thickened. The tricuspidal annulus was modestly (3 FB) enlarged. MV replacement with a #31 Carpentier-Edwards bioprosthesis and tricuspidal annuloplasty with Kay's methods were carried out uneventfully. He was readily weaned from the CPB with the aid of dopamine (5$\mu g \cdot kg^{-1} \cdot min^{-1}$). M-PNL (1240 mg) was administered intravenously after discontinuation of the CPB. The post-CPB period was also uneventful: no apparent hemorrhagic tendency was observed after heparin reversal. Arterial blood gas analyses, auscultation of the chest, and chest radiograph did not suggest any evidence for intraoperative occurrence of pulmonary edema. No significant increase in the peripheral eosinophil counts was observed intraoperatively (Fig. 1). He was transferred to the Intensive Care Unit in satisfactory condition. His postoperative course in the ICU was

uneventful. The next morning, he was discharged from the ICU after his trachea was extubated. Postoperatively, both in the ICU and the ward, the steroid therapy with PNL had been continued to prevent the increase in the eosinophil counts. Since the eosinophil counts began to increase on the 3rd day after the operation despite the steroid therapy, HU was added to the therapy for the eosinophilia from the 5th day after the operation (Fig. 1). Despite a modest increase in the eosinophil counts (Fig. 1), no significant organ system dysfunction was observed postoperatively in the ward. At the time of this writing, he is in his 5th postoperative month and is doing well.

Discussion

IHS is a group of disorders characterized by prolonged eosinophilia of unknown etiology associated with multiple organ system dysfunction [2]. The organ dysfunction is secondary to eosinophilic infiltration of the organ or eosinophil-mediated tissue injury [1–3]. Cardiac involvement is known to occur in approximately 50% of the patients and to be the major cause of morbidity and mortality of this syndrome [4]. A characteristic cardiac primary lesion is endocardial fibrosis superimposed with ventricular mural thrombosis, which was first described by Löffler in 1936 as a cardiac lesion associated with eosinophilia [6] and has been called Löffler's endocarditis. Endocardial biopsies on our patient performed 13 months prior to the admission had also revealed endocardial fibrosis. The thrombotic process possibly leads to restrictive cardiomyopathy or a restriction of the valve leaflet, which may cause ventricular or valvular dysfunction. The most commonly observed valvular dysfunction in the IHS is atrioventricular regurgitation, and this was also observed in our patient. Valve replacement may be appropriate if either extracardiac manifestations of the eosinophilic process are controlled, if the underlying cardiomyopathy is not severe, or if the cardiac involvement is localized [5]. The extracardiac organ involvement can include brain, lung, vessels, reticuloendothelial system, gut and skin, being clinically manifested as pulmonary fibrosis, hepatosplenomegaly, thrombosis, etc. [2,4,7–9]. Lung involvement is common, with cough, dyspnea and pyrexia in up to 40% of all cases [1]. Our patient developed a dry cough 8 years ago which persisted up to about 1 year prior to the admission, and transbronchial lung biopsies performed 13 months prior to the admission revealed eosinophilic infiltration of the interstitial and alveolar space. However, there was no clinical evidence of either pulmonary fibrosis or dysfunction before the operation. Although our patient also had hepatosplenomegaly and had previously suffered from both thromboembolic event and abdominal symptoms, there was no sign of any deterioration in these conditions before the operation. Furthermore, his eosinophilia had been controlled with the above-mentioned medication (Fig. 1). Finally, the underlying cardiomyopathy seemed mild based on the echocardiogram and cardiac catheterization. Valve replacement, therefore, seemed to be the best choice to improve his cardiac condition and his prognosis, although to our knowledge there has been no formal study which has demonstrated the long-term benefit of surgical intervention for this syndrome.

Although the surgical experience of patients with cardiac involvement secondary to IHS are limited [7], prosthetic valve malfunction has been reported as one of the postoperative complications in patients with IHS who underwent valve replacement [5,7,10]. Hendren et al. [5] and Boustany et al. [7] have reported repeated occurrences of prosthetic valve malfunction after valve replacements in patients with IHS; the onset dates varied from 3 days to 26 months after the valve replacement [5,7]. These patients have been treated with valve re-replacement with bioprosthesis in place of mechanical prosthesis, thrombectomy of the prosthesis, controlling eosinophilia by steroid or HU, or anticoagulants [5,7]. Their intraoperative findings at the second operation and the effectiveness of controlling eosinophilia in treating the valve dysfunction in these patients have strongly suggested that the valve dysfunction was due to an involvement of the prosthetic valve leaflets with eosinophilic vegetation [5,7,10]. These authors have recommended that, in order to minimize the risk of prosthetic valve thrombosis, (1) the efforts to reduce peripheral eosinophil counts must be maximized, (2) if possible, the valve replacement should be performed using a bioprosthesis, and (3) a regular follow-up for signs of valve dysfunction is necessary, particularly during episodes of rising or uncontrolled eosinophilia [5,7,10].

On the other hand, severe postoperative complications have also been reported in patients with IHS who underwent noncardiac surgery [8]. Samsoon et al. recently reported severe respiratory failure occurring after general anesthesia in two patients with markedly increased eosinophil counts, in whom IHS was diagnosed after the operation [8]. One patient developed life-threatening respiratory failure due to increased pulmonary vascular permeability and severe bronchospasm in the immediate postoperative period, and required mechanical ventilation for about 20 days after operation with the diagnosis of adult respiratory distress syndrome (ARDS) [8]. The other patient developed coagulopathy due to severe thrombocytopenia 12 h after the operation, and later severe respiratory failure after 7 days [8]. Control of the marked eosinophilia ($16.75–59 \times 10^9$ liter^{-1}) with steroids appeared to be effective in improving their respiratory

status in both patients [8]. The authors suggested that the observed respiratory problems were associated with lung damage produced by eosinophil degranulation, and they recommended that a perioperative steroid cover may be an effective precaution to minimize the risk in any patient presenting with a greatly increased eosinophil count before operation [8]. The absence of any significant complications intra- and postoperatively in our patient might have been due to our intensive control of the eosinophilia using steroids and HU during the perioperative period.

Eosinophil-mediated tissue injury has been thought to be due to a local deposition of various eosinophil-derived cytotoxic substances, such as the major basic proteins, eosinophilic cationic proteins (ECP), leukotriene C, free oxygen radicals, and a variety of enzymes (e.g. collagenase, lecithinase), which are known to be released from activated eosinophils as a result of their degranulation [11–13]. Endogenous cationic proteins, released by inflammatory cells into lung circulation, have been proposed to cause lung microvascular damage by neutralizing and removing negative charges on the endothelial cell surface of pulmonary microvasculature, and to play a key role in the development of ARDS, in which lung microvascular injury represents one of the central pathophysiologic events, through a mechanism largely independent of oxygen-derived radicals and proteolytic pathways [14]. Activated eosinophils have also recently been shown to increase vascular permeability in the isolated rat lung [15,16], and markedly increased ECP levels in both serum and bronchoalveolar lavage fluid have been demonstrated in patients with ARDS [17]. The respiratory problems that occurred in their patients with IHS after general anethesia reported by Samsoon et al. were probably due to such eosinophil-mediated lung microvascular injury just as the authors suggested [8]. Postperfusion lung syndrome (PPLS) or noncardiogenic pulmonary edema are known as respiratory complications after cardiac surgery [18,19]: the endothelial or epithelial cell injury or significant increase in lung water have been observed in the PPLS, which is now recognized to be merely another type of ARDS [20,21]. Patients undergoing cardiac surgery with CPB are, therefore, more susceptible not only to cardiogenic but to noncardiogenic pulmonary edema after operation than those undergoing noncardiac surgery. Since severe respiratory failure in the postoperative period were reported even in the patients with IHS who underwent noncardiac surgery [8], the perioperative intensive control of the eosinophilia must be particularly important for the patients with IHS who undergo cardiac surgery not only to prevent prosthetic valve malfunction but also to minimize the risk of postoperative respiratory failure. At present, the mainstay of treatment of the eosinophilia in IHS seems to be steroids, which are known to inhibit eosinophil chemotaxis, adherence, and degranulation, and has been shown to actually be effective in decreasing the eosinophil counts as well as in improving the organ dysfunction associated with the eosinophilia in IHS in the previous studies and also in our patient [5,6,8]. In addition to the steroids, HU and IFN, used in our patient, have also been proved useful in controlling IHS [3,22,23].

In conclusion, we presented a patient with IHS who underwent mitral valve replacement and tricuspidal annuloplasty for cardiac involvement secondary to IHS. His intra- and postoperative course was uneventful and until now he has not suffered any significant complications, such as respiratory failure, coagulopathy, or prosthetic valve dysfunction, which have previously been reported as the major postoperative complications in IHS [5,7,8]. Such satisfactory perioperative course might be due to our intensive control of the eosinophilia with steroids and hydroxyurea in the perioperative period (beginning in the preoperative period). Furthermore, no significant increase in the eosinophil counts were observed intraoperatively, but about a 50% decrease in the eosinophil counts was observed after the initiation of CPB (hypothermia) probably due to the dilutional effects. The intensive control of the eosinophilia in the perioperative period with steroids or hydroxyurea is probably beneficial to minimize the perioperative risk in patients with IHS.

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