GENERAL ANAESTHESIA AND THE HYPEREOSINOPHILIC SYNDROME: SEVERE POSTOPERATIVE COMPLICATIONS IN TWO PATIENTS

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SUMMARY
Two patients with markedly increased eosinophil counts developed severe postoperative complications after general anaesthesia. One patient suffered life-threatening Adult Respiratory Distress Syndrome (ARDS), while the other presented with a coagulopathy and less severe respiratory problems. The hypereosinophilic syndrome is described and the possibility of a role of eosinophils in the pathogenesis of tissue injury is discussed. These cases suggest that, in patients with marked eosinophilia requiring general anaesthesia, perioperative steroid cover is advisable. This may reduce or prevent serious lung damage and other complications. (Br. J. Anaesth. 1992; 69: 653-656)

KEY WORDS
Anaesthesia, general. Complications: hypereosinophilic syndrome. Lung: ARDS.

We describe two patients who developed severe postoperative complications in association with very high eosinophil counts. The problems had not been anticipated in view of the absence of pre-existing pathology and the type of surgery involved. These cases highlight the potential for eosinophils to cause tissue injury and raise the possibility of their involvement in the pathogenesis of the Adult Respiratory Distress Syndrome.

CASE REPORTS

Patient No. 1
A 14-yr-old schoolboy was referred for investigation of hepatosplenomegaly and eosinophilia. He gave a 7-week history of watery diarrhoea, malaise, anorexia and weight loss. He was thin, with a few enlarged cervical lymph nodes and three discrete necrotic skin lesions. Marked hepatosplenomegaly was found, but the remainder of the examination was normal. Investigations revealed:

- haemoglobin 11.5 g dl⁻¹
- WBC 63 × 10⁹ litre⁻¹ (34 % eosinophils, 47 % neutrophils, 11 % lymphocytes, 8 % monocytes)
- platelets 300 × 10⁹ litre⁻¹
- Serum urea and electrolyte concentrations were normal:
- alkaline phosphatase 323 iu litre⁻¹
- alanine transaminase 57 iu litre⁻¹
- total protein 102 g litre⁻¹
- albumin 22 g litre⁻¹

The chest radiograph was normal on admission. Abdominal ultrasound confirmed a greatly enlarged liver of homogenous texture and showed chains of enlarged para-aortic and pericaval lymph nodes. A provisional diagnosis of myeloproliferative disease or lymphoma was made and it was decided to proceed to insertion of a Hickman line, posterior iliac crest bone marrow aspirate and liver biopsy under general anaesthesia.

The anaesthetic technique consisted of premedication with temazepam and metoclopramide, induction with fentanyl 4 µg kg⁻¹, propofol 2 mg kg⁻¹ and atracurium 0.7 mg kg⁻¹ before intubation, maintenance with nitrous oxide-oxygen-isoflurane, increments of atracurium and IPPV. The inspired oxygen fractional concentration was 0.35 and the arterial oxygen saturation measured by pulse oximetry was 100% throughout. The procedure was uneventful.

In the hours after the operation, the patient became pyrexial (39 °C) and tachypnoeic with a dry cough. Auscultation of the chest was normal and there was no other clinical sign of infection. Gentamicin and azlocillin were commenced empirically. Twenty-four hours later, the tachypnoea had worsened (50 b.p.m.) and he was cyanosed whilst breathing air. The chest radiograph on the first day after operation showed widespread alveolar shadowing. He was hypoxaemic and anaemic with a haemoglobin concentration of 7.8 g dl⁻¹. The differential diagnosis lay between opportunistic infection and eosinophilic pulmonary infiltration. Sputum cultures for acid fast bacilli, bacterial and atypical pathogens were performed. Blood and stool cultures and antibody screens were also undertaken. The bone marrow was hypercellular with marked eosinophilia, although maturation was normal. Liver biopsy showed inflammation in the portal zones with piecemeal necrosis, polymorph infiltration and fibrosis. There was no sign of arteritis in the specimen. The blood film showed increased de-
granulation of circulating eosinophils: the number of degranulated eosinophils increased from $13.25 \times 10^8$ litre$^{-1}$ before operation to $17.1 \times 10^8$ litre$^{-1}$ after operation (a 29% increase), with no change in the total white cell count. Erythromycin and i.v. hydrocortisone 100 mg 6-hourly were added to the drug regimen.

The patient later developed bilateral fine basal inspiratory crepitations with worsening hypoxaemia and exhaustion. Severe Adult Respiratory Distress Syndrome (ARDS) was diagnosed and 48 h after operation he required mechanical ventilation. An $F_{1O_2}$ of 1, tidal volume 20 ml kg$^{-1}$ and PEEP of 15 cm H$_2$O were needed to maintain the arterial oxygen saturation between 85 and 90%. Blood-stained, frothy sputum was aspirated from the tracheal tube. Increased airway tone and reactivity were manifested by widespread bronchospasm and increased inflation pressures requiring nebulized salbutamol. Pulmonary artery catheter pressures (right ventricular $33/0$ mm Hg, pulmonary artery $30/15$ mm Hg, pulmonary capillary wedge pressure $14/3$ mean $5$ mm Hg), were consistent with non-cardiogenic pulmonary oedema (fig. 1). He was shocked and oliguric, requiring frequent colloid infusion and inotropic support. Blood cultures remained negative. I.v. methyl prednisolone was started because of the prolonged normal peripheral blood eosinophil count and the clinical course make this diagnosis unlikely.

Patient No. 2

A 52-yr-old man was admitted complaining of epigastric pain, nausea and vomiting. He had no significant past medical history and smoked 40 g of pipe tobacco per week. He was apyrexial, cardiorespiratory examination was unremarkable and he had guarding and rebound tenderness in the right iliac fossa. Investigations showed: Hb 14.6 g dl$^{-1}$, WBC $25.7 \times 10^9$ litre$^{-1}$, serum concentrations of urea, electrolytes and amylase normal. There was no clinical evidence of haemorrhagic tendency. The chest radiograph was clear. Appendectomy was planned for the same day.

He was premedicated with pethidine and atropine. A rapid sequence induction technique was used with thiopentone and suxamethonium. Anaesthesia was maintained with nitrous oxide, oxygen, halothane and intermittent boluses of alcuronium. Emergency appendectomy was carried out uneventfully. The specimen was macroscopically normal and histology was not requested.

Twelve hours after operation, there was considerable blood loss from the surgical wound, the patient developed tachycardia and hypotension and required blood transfusion. Further examination of the preoperative blood sample showed that 65% of WBC were eosinophils (16.75 $\times 10^9$ litre$^{-1}$) and a platelet concentration of $16 \times 10^9$ litre$^{-1}$. The coagulation screen was normal. Platelet transfusion was carried out.

On the first day after operation, bone marrow aspiration yielded a sample with increased cellularity and 45% eosinophils, 10% at the eosinophil myelocyte stage. Megakaryocytes were reduced and reduced. His exercise tolerance was severely limited because of large emphysematous bullae compressing the remaining lung tissue. Slow improvement continued and he was discharged on the 47th day, receiving prednisolone 15 mg daily, his eosinophil count having decreased to zero. An echocardiogram performed before discharge showed hyperechogenic areas within the myocardium, consistent with eosinophilic "microabscesses". Valvular function was normal. Investigations for viral, parasitic and opportunistic infections remained negative. Electrophoresis of serum proteins before discharge showed a slight increase in $\alpha_1$ globulins with total proteins $65$ g litre$^{-1}$ and albumin $32$ g litre$^{-1}$.

Six weeks later, the patient's spleen and liver were no longer palpable and there was no lymphadenopathy. His exercise tolerance was improving. The eosinophil count continued to fluctuate over the following 9 months and was controlled with varying doses of oral prednisolone and intermittent i.v. vincristine. Thereafter, the eosinophil count returned to normal and during 3 years follow up he has remained well apart from minor bowel upset controlled by low dose prednisolone. The possibility of an underlying myeloproliferative disorder such as chronic granulocytic leukaemia has not been excluded by repeat bone marrow and chromosome analysis, but the prolonged normal peripheral blood count and the clinical course make this diagnosis unlikely.
platelet budding was scant. Possible diagnoses considered were a leukaemic disorder, advanced parasitic disease, polyarteritis nodosa and hypereosinophilic syndrome. Extensive investigations for parasitic infection, connective tissue disorders and other conditions associated with eosinophilia were negative.

On the second day after operation prednisolone 10 mg three times daily was commenced and further blood and platelet transfusions were required. On day 7, the patient was found to be tachypnoeic (ventilatory frequency 30 b.p.m.), tachycardic (160 beat min⁻¹) and centrally cyanosed. He was transferred to the Intensive Care Unit where he was given 100 % oxygen by mask. Blood-gas analysis revealed a pH of 7.3, \( P_{aO_2} \) 8.1 kPa, \( P_{aCO_2} \) 4.2 kPa. The chest radiograph showed bilateral diffuse shadowing consistent with alveolar exudation. He was given i.v. hydrocortisone 100 mg four times daily. His respiratory status improved over 48 h and he was fit for transfer to a general ward. At this stage his platelet count began to improve and increased slowly to normal values during the next 5 weeks.

Whilst receiving steroid treatment, the patient required two further general anaesthetics for resutting of abdominal wall dehiscence. Both procedures were uneventful. He was finally discharged 7 weeks after admission.

Over the next 5 years, he continued to have increases in his eosinophil count controlled with varying doses of prednisolone. He maintained a normal platelet count and at no time was there development of a leukaemic disorder or other condition associated with eosinophilia.

**DISCUSSION**

An increase in the total blood eosinophil count may occur in association with a large variety of conditions. Worldwide, the most important cause of eosinophilia is parasitic infection, but allergy, skin disease, neoplasia and drugs are common causes. The increase in cell numbers is usually mild or moderate. Occasionally, however, greatly increased counts (20–40 \( \times 10^9 \) litre⁻¹) may be seen [1].

Although the eosinophil was identified by Ehrlich more than a century ago, its role in disease has been recognized only recently. It was assumed previously that eosinophils played a beneficial role in host defence against parasitic infections and in downregulation of the inflammatory process after immediate-type hypersensitivity reactions. However, as the toxicity of the eosinophil to human tissue has become evident in the past decade, this cell is now increasingly regarded as a potent proinflammatory agent with considerable tissue-damaging potential and a mediator of epithelial injury and bronchial hyperreactivity [2]. It is also recognized as producing endomyocardial fibrosis in Loeffler’s disease [3].

The hypereosinophilic syndrome was described first in 1968 by Hardy, who associated a range of complications with persistent eosinophilia [4]. The criteria for the hypereosinophilic syndrome (HES) were defined later by Chusid and colleagues [5] as:

- eosinophilia > 2.5 \( \times 10^9 \) litre⁻¹; persistent eosinophilia for at least 6 months unless fatal in the shorter term; organ involvement and dysfunction; no other recognizable cause of eosinophilia. The syndrome is rare, occurring more commonly in men than in women (male:female ratio 9:1) [1]. The mode of presentation is varied. Rarely (10 %), it is an incidental finding. However, lung involvement is common, with cough, dyspnoea and pyrexia in up to 40 % of cases [6]. ARDS complicating the hypereosinophilic syndrome has not previously been described.

Our first patient represents a severe form of the hypereosinophilic syndrome, with multiple system involvement, including lung, skin, gut, reticuloendothelial and cardiovascular systems, requiring 3 weeks of life support in Intensive Care. In the second patient, the part played by the very high eosinophil count in the postoperative respiratory complications was less clearly defined because of the associated thrombocytopenia. Decreased platelet counts have been reported in the hypereosinophilic syndrome [7]. Pulmonary capillary pressure was not measured in this patient and the pulmonary problem occurred several days after anaesthesia. Pulmonary haemorrhage, sepsis or fluid overload could have been responsible for the symptoms, but the rapid resolution of the respiratory distress following the start of high-dose parenteral steroids without diuretic or antimicrobial therapy supports the significant contribution of the eosinophila.

The mechanism of tissue damage by eosinophils is related to the large intracytoplasmic granules which, when activated, release a variety of cytotoxic mediators. The most important of these are major basic protein (MBP), eosinophilic cationic protein (ECP), leukotriene \( C_4 \) and oxygen free radicals [2, 8]. There is also release of a variety of enzymes, including collagenase and lecithinase. An important finding in HES is vacuolation and degranulation of the circulating eosinophils, whereas bone marrow eosinophils in these patients do not show such changes. It is proposed that both the normal effector mechanisms of eosinophils in parasitic infections and the tissue damage induced in HES are secondary to peripheral degranulation with release of MBP and other mediators [8]. Indeed, the presence of vacuolation has been correlated with the extent of tissue damage [6]. In patient No. 1 reported here, the number of degranulated circulating eosinophils increased by 29 % after operation. Ayars and colleagues have shown that activated eosinophils can provoke detachment type injury at the pneumocyte layer of the alveolar membrane. This causes membrane breakdown, with efflux of cells and proteins into the alveolus, leading to low pressure pulmonary oedema [9]. Moreover, Hallgren and co-workers have demonstrated markedly increased concentrations of ECP in both serum and bronchoalveolar lavage fluid in patients with ARDS, while the concentration of ECP correlated with the severity of ARDS [10]. Recently, eosinophils have been shown experimentally to increase vascular permeability and resistance in isolated rat lungs [11, 12] and ECP is known to cause increase Airways reactivity and tone
Our first patient presented with both increased pulmonary vascular permeability and severe bronchospasm. We suggest that this patient's respiratory problems were associated with lung damage produced by eosinophil degranulation. In the second patient, respiratory failure could have been precipitated by various causes but, in our opinion, eosinophils most probably played a part. These patients illustrate how eosinophil-mediated damage may represent an alternative mechanism to the well established neutrophil-mediated pathway [14, 15] in the pathophysiology of the Adult Respiratory Distress Syndrome.

The mainstay of treatment in the hyper-eosinophilic syndrome is steroids. These drugs inhibit eosinophil chemotaxis, adherence and degranulation, thus preventing the release of cytotoxic mediators. In addition, they gradually deplete the marrow of eosinophil reserves. The use of steroids in the treatment of ARDS is still controversial. In the past few years they have been considered unhelpful and to increase the risk of infection [16]; however, recent reports have demonstrated a possible beneficial effect of steroids in this syndrome [17]. The role of steroids in septic states is equally unclear, despite two recent randomized controlled trials on this subject [18, 19]. In these trials, no overall reduction in mortality was demonstrated in the steroid-treated patients, although patients with gram-negative sepsis treated with steroids had a better prognosis. Steroids, however, tended to increase the incidence of secondary infections in all patients. In the two patients reported here, steroid treatment promoted relatively rapid recovery of the severe respiratory symptoms, but the first case was complicated by serious secondary infection. Steroids are not always successful in the treatment of HES. Vincristine and hydroxyurea have proven useful in aggressive disease [7]. Our first patient was controlled successfully after the acute phase with a combination of steroids and intermittent i.v. vincristine. Recently, reports of a beneficial effect of interferon in the treatment of the HES have been published [20, 21].

In conclusion, these two patients illustrate two important notions: first, the cytotoxic potential of the eosinophil, with the possibility of triggering severe lung damage that can lead to the development of ARDS; second, the risk for patients presenting with hypereosinophilia of developing major complications after general anesthesia. We suggest that perioperative steroid cover may be an important precaution to minimize the risk in any patient presenting with a greatly increased eosinophil count before operation.