NATURAL KILLER CELL ACTIVITY IN A PATIENT UNDERGOING RESECTION OF PHAEOCHROMOCYTOMA

E. TØNNESEN, F. KNUDSEN, H. K. NIELSEN AND N. J. CHRISTENSEN

Natural killer (NK) cells were discovered in the mid-1970s, because of their capacity to kill directly tumour cell lines, infected host cells and some normal cell types [1,2]. They are potentially important in protection against tumour cells and infections, and in immunoregulation, although their exact role in vivo remains to be clarified [3].

NK cell activity is depressed after major surgery, while a transient increase in activity has been demonstrated during the early stages of anaesthesia and surgical procedures [4-9]. The endocrine stress response to surgery seems to be important [9,10]. Serum cortisol and plasma adrenaline are prominent markers of this response and several studies have demonstrated that adrenaline enhances NK cell activity in vitro and in vivo [11-13], while corticosteroids inhibit activity [14,15].

Phaeochromocytoma is a rare tumour which secretes catecholamines, often in massive quantities. This report describes the relationship between plasma catecholamine concentrations and NK cell activity in vivo.

CASE REPORT

The patient was an otherwise healthy 35-year-old woman (weight 68 kg) with a phaeochromocytoma demonstrated by angiography and hormone analysis. She was admitted to the intensive care unit on the day before operation. A central venous catheter, a lumbar extradural catheter and an arterial cannula were inserted using local analgesia, and arterial and central venous pressure and cardiographic monitoring were established. No premedication was given, at the request of the patient. Three hours before operation, extradural analgesia was induced with 0.5% bupivacaine 5 ml every 10 min until analgesia, tested by pinprick, extended from S5 to T4 (a total of 25 ml of bupivacaine).

Anaesthesia was induced with fentanyl 0.3 mg and etomidate 26 mg, and neuromuscular block was achieved with pancuronium 8 mg. Anaesthesia was maintained with 0.5-2% isoflurane and 66% nitrous oxide in oxygen. Supplementary doses of fentanyl and pancuronium were given as needed. Extradural analgesia was maintained with incremental doses of 0.5% bupivacaine 5 ml every 1 h. The patient underwent mechanical ventilation using a Servo ventilator. At the end of operation, residual neuromuscular blockade was antagonized with neostigmine 2.5 mg preceded by atropine 1 mg.

The durations of anaesthesia and surgery were 160 min and 110 min, respectively. Hypertension with mean arterial pressure (MAP) up to 155 mm Hg occurred during tumour manipulation and removal, and was controlled with infusions of nitroglycerin and phentolamine. Hypotension
Fig. 1. NK cell activity, percentage of Leu 11+ cells, and plasma adrenaline and noradrenaline concentrations in a patient undergoing resection of phaeochromocytoma. Blood samples are indicated by arrows. Sample 1 = before operation and extradural analgesia; 2 = before induction of general anaesthesia; 3 = during general anaesthesia; 4 = immediately after tracheal intubation; 5 = just before skin incision; 6 = after skin incision; 7 = tumour manipulation and removal; 8 = completion of surgery; 9 = 6 h after skin suture; 10 = first day after operation.

(MAP 45 mm Hg) was noted just after the tumour was removed, and was treated with fluid infusions and dopamine. The postoperative course was uneventful.

Arterial blood was sampled for determination of NK cell cytotoxicity, distribution of Leu 11+ cells, and measurement of plasma adrenaline and noradrenaline concentrations as indicated in figure 1. Plasma catecholamine concentrations were measured by a single isotope-derivative assay [16].

NK cell cytotoxicity assay

Separation of mononuclear cells, cryopreservation, and determination of NK cell cytotoxicity were performed as described previously [5]. Briefly, mononuclear cells were isolated by Ficoll-Hypaque (Lymphoprep, Nyegaard & Co., Oslo)
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gradient centrifugation. The cells were cryopreserved and stored in liquid nitrogen until all specimens from the patient could be tested simultaneously against K562 target cells in a 6-h chromium-51 release assay. All assays were performed in duplicate at effector to target cells ratios of 50:1, 25:1 and 12.5:1; results represent the 50:1 ratio. NK cell activity was expressed as percentage cytotoxicity according to the expression: % cytotoxicity = [(cpm experimental release—cpm spontaneous release)/(cpm maximum release—cpm spontaneous release)] x 100, where cpm = counts min⁻¹; spontaneous release = radioactivity released from target cells in the growth medium; maximum release = radioactivity generated when the target cells were frozen and thawed three times in distilled water. The spontaneous release was 15% of the maximum release.

Lymphocyte subpopulation (Leu 11+ cells)

The relative percentage of NK cells in peripheral blood mononuclear cells was estimated by the use of the monoclonal antibody Leu 11 (Becton Dickinson, California) reacting selectively with NK cells [8].

RESULTS

The changes in NK cell activity, percentage of Leu 11+ cells, and plasma catecholamine concentrations are shown in figure 1. Intubation of the trachea and tumour manipulation were associated with rapid and marked increases in plasma adrenaline and noradrenaline concentrations and in NK cell activity. The percentage of Leu 11+ cells also increased after intubation. Too few cells were obtained to permit accurate enumeration of Leu 11+ cells during tumour manipulation.

DISCUSSION

Surgical manipulation and removal of phaeochromocytoma may provoke excessive release of catecholamines and, accordingly, would be expected to induce acute peroperative changes in NK cell activity. This clinical report confirms the role of adrenaline as a potent stimulator/inducer of NK cell cytotoxicity in vivo [8,11,13]. Furthermore, the results suggest a positive correlation between NK cell activity and the number of circulating Leu 11+ cells. The increase in NK cell activity, at least after intubation of the trachea, may be explained by an increase in the number of circulating NK cells.

In a previous study of patients undergoing coronary artery bypass grafting, intubation of the trachea was not accompanied by an increase in plasma adrenaline or noradrenaline concentrations, but by a small but significant decrease [8]. Although plasma catecholamine concentrations increased markedly after intubation of the trachea in the present patient, no comparison is possible because of differences in the underlying diseases and anaesthetic techniques used.

All normal individuals have active NK cells, with the highest activity observed in blood and spleen. There are great interindividual variations in NK cell activity with low and high responders and also some linkage to certain MHC (major histocompatibility complex) haplotypes, sex, age, smoking, exercise and other systemic factors [17]. In the present patient NK cell activity was low both before and after operation.

In contrast with other cytotoxic cells, such as T-lymphocytes and monocytes, NK cells can be mobilized or activated within minutes. The NK cell system, therefore, together with the sympatho-adrenal system, may participate in the general pattern of reactions to stress and harmful or noxious stimuli. The NK cell system may thus rapidly enhance the defence of the organism against tumours and microorganisms.

The present case report has added further evidence to the concept that catecholamines acutely regulate NK cell activity during anaesthesia and surgery.

REFERENCES

6. Tennesen E, Hützel MS, Christensen NJ, Schmitz O. Natural killer cell activity in patients undergoing upper abdominal surgery: Relationship to the endocrine stress