Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Sensory neuropathy in paraneoplastic leucocytosis

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Summary

Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) sensitise nerves to mechanical stimuli experimentally and may induce bone and muscle pain when used as supportive drugs. G-CSF and GM-CSF produced endogenously by tumour cells can cause paraneoplastic leucocytosis. Whether paraneoplastic leucocytosis is associated with changes in pain sensitivity is not yet clear. We report on a patient with advanced-stage thyroid cancer who developed extreme leucocytosis within a period of 4 weeks (103 000 white blood cells/mm³), composed mostly of neutrophils and eosinophils. Parallel to this leukemoid reaction, allodynia and hyperalgesia developed in the absence of tissue inflammation. The course of disease of an elderly male with advanced stage metastatic thyroid cancer with new onset neuropathic pain followed by the development of extreme leucocytosis in a leukemoid reaction suggests paraneoplastic release of myeloid CSFs. The coincidence of pain sensitisation and extreme leucocytosis suggests a causal contribution of G-CSF and GM-CSF.

BACKGROUND

Glial-derived factors, inflammatory mediators and their coupled signalling pathways probably play an important role in the modulation of neuropathic pain for which the paradigm is shifting from a single mediator towards a system of mediators. Examples of mediators include the chemokine system and cytokines.¹ Receptors and signalling mediators of granulocyte-macrophage and granulocyte-macrophage colony-stimulating factors (G-CSF and GM-CSF) are functionally expressed on sensory nerves and sensitise nerves to mechanical stimuli in vitro and in vivo.² Pain is also the most relevant side effect of G-CSF administration in healthy donors of bone marrow stem cells and cancer patients; exogenous recombinant G-CSF may cause bone pain and myalgia via mechanisms that may involve G-CSF-induced inflammatory neuronopathy.^{3 4}

G-CSF and GM-CSF are released into systemic circulation paraneoplastically in patients with solid tumours causing extreme leucocytosis via their effects on bone marrow.⁵ As infection is an uncommon cause of extreme leucocytosis in patients with solid tumours, such paraneoplastic 'leukemoid reactions', characterised by marked neutrophilia and often eosinophilia, are typically seen in patients who are clinically stable despite having large tumour burdens; however, clinical outcomes are poor unless effective antineoplastic treatment is given.⁵ In such patients, paraneoplastic G-CSF and GM-CSF might also cause pain.

CASE PRESENTATION

On 25 December 2011 a 90-year-old man was referred to us with a 4-week history of dyspnoea. He had undergone total thyroidectomy for papillary thyroid cancer at the age of 79 years. In 2007, he had received a course of I¹³¹

radiotherapy for multiple skeletal, pulmonary and mediastinal metastases.

Four weeks earlier, the patient had been admitted to the hospital's palliative care unit because of an increase of mild chronic retrosternal pain due to metastases in the mediastinum that was associated with the sensation of needles and pins and new onset of superficial mechanical hyperalgesia particularly of the trunk and also of upper extremities and the abdomen for which oxycodone/naloxone at a dose of 10/5 mg every 12 h in combination with pregabalin 25 mg every 12 h was initiated, but with little effect. Because of the potentially inflammatory nature of pain, dexamethasone 21-(disodium phosphate) was additionally given at a daily dose of 2 mg. A white blood cell count (WBC) of 12 500/mm³ had been noted initially with no signs of infection. After 2 weeks, the patient was discharged to outpatient care despite increasing WBCs.

After discharge from the palliative care unit, the patient had developed pathological radius fracture, which was orthopedically treated. Blood test performed at that time showed that WBC had increased to 33 680/mm³. Of the total WBC, 48% were neutrophils and 16% eosinophils. Despite continued treatment with oxycodone/naloxone, pregabalin and dexamethasone, pain persisted. Pregabalin was considered ineffective and stopped. During the following 2 weeks after discharge from the hospital, the patient developed extreme leucocytosis. The patient was then readmitted to hospital.

INVESTIGATIONS

On admission, WBC was 103 000/mm³, C-reactive protein was moderately elevated to 6.5 mg/dl (normal range, <0.5 mg/dl) and the erythrocyte sedimentation rate was 48 mm after the first hour (normal range, <35 mm) with no evidence of underlying infection.

Global respiratory insufficiency was present and attributed to pleural effusions and pulmonary infiltrates due to cancer metastasis and pneumonitis seen on chest x-ray. Light touch of the trunk and upper extremities was perceived as painful, and pinprick became extremely painful in areas with no signs of inflammation. Nerve conduction studies and quantitative sensory testing were not performed because of restriction to palliative end-of-life care.

TREATMENT

The patient was treated symptomatically with oxygen supplementation and increasing doses intravenous morphine. Old age and the terminal stage of thyroid cancer precluded transfer to the intensive care unit for treatment of acute respiratory distress syndrome.

OUTCOME AND FOLLOW-UP

The patient died 2 days after admission.

DISCUSSION

Paraneoplastic neuropathic pain is generated by electrical hyperactivity of neurons along the pain pathways. Peripheral mechanisms are more frequently involved than central mechanisms, and include primary sensitisation of nerve endings by tumour-derived mediators. In the present case, the quality of pain presented as abnormal pain (allodynia and hyperalgesia).

Paraneoplastic leucocytosis is seen in patients with lung, gastrointestinal, genitourinary or head and neck cancers, but rarely occurs in thyroid carcinoma.^{5 6} As in other solid tumours, leukemoid reactions are caused by abnormal production of haematopoietic cytokines from tumour cells including GM-CSF and G-CSF also in thyroid cancer patients.⁷ Circulating levels of G-CSF and GM-CSF were not measured directly in our patient; however, sensory neuropathy of new onset and its persistence during the development of extreme leucocytosis in a patient whose WBCs had always been in the normal range below 10 000/mm³ as documented over several years makes it very likely that paraneoplastic release of myelopoietic growth factors was in fact responsible also for his increased pain sensitivity.

As frequently seen in patients with paraneoplastic neuropathic pain, analgesic therapy was not adequate in our patient too. Whether this is due to the specific pathomechanisms of this syndrome that might include receptors and signalling mediators of G-CSF and GM-CSF

which are functionally expressed on sensory nerves^{2 3} needs elucidation in further studies. Anti-G-CSF and anti-GM-CSF strategies may be potential novel drug targets in neuropathic pain.

This case of an elderly patient with advanced-stage metastatic thyroid cancer with new-onset mechanical hyperalgesia followed by the development of extreme leucocytosis in a leukemoid reaction suggests paraneoplastic release of myeloid CSFs. The coincidence of hyperalgesia and extreme leucocytosis suggests a causal contribution of G-CSF and GM-CSF.

Learning points

- ▶ Paraneoplastic release of myelopoietic growth factors may cause hyperalgesia.
- ▶ Leukemoid reactions occur in thyroid carcinoma.
- ▶ The coincidence of sensory neuropathy and extreme leucocytosis suggests a causal contribution of granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor.

Competing interests None.

Patient consent Obtained.

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