Paraneoplastic syndromes

Background

Paraneoplastic syndromes are defined as clinical syndromes involving non-metastatic systemic effects that accompany malignant disease. The symptoms may be endocrine, neuromuscular, musculoskeletal, cardiovascular, cutaneous, haematologic, gastrointestinal, renal, or a mix of these. This CME series focuses on dermatological, endocrine and neurological manifestations.

People of all ages may be affected by cancer and its paraneoplastic syndromes. There is no gender or race predilection. These syndromes occur in about 10-15% (2-20% according to some reports) of malignancies, and may be the first or most prominent manifestation. Although data are not available, the incidence of paramalignant syndromes in Sri Lanka should not be underestimated. It is likely that many are undiagnosed for reasons such as lack of awareness and inadequate investigation.

Pathophysiology

Currently the mechanisms of how cancers affect distant sites are not completely understood. When a tumour arises, the body may produce antibodies to fight it by binding to and destroying tumour cells. Unfortunately, in some cases, these antibodies cross-react with normal tissues and damage or destroy them, which may stimulate the onset of paraneoplastic disorders. But, not all paraneoplastic syndromes are associated with antibodies.

Any tumour may produce hormones and hormone precursors, a variety of enzymes and foetal proteins, or cytokines. More rarely, the tumour may interfere with metabolic pathways or steroid metabolism. In some paraneoplastic syndromes the pathophysiology may not be clear.

Several cancers produce foetal proteins that are physiologically expressed in embryonic cells during foetal life but not by normal adult cells. These substances may help clinicians detect malignancies and are used as tumour markers (eg. carcinoembryonic antigen [CEA], alpha-fetoprotein [AFP], cancer antigens [CA 19.9]).

Clinical manifestations

Paraneoplastic syndromes may evolve over weeks to months (rarely, 1-3 years) and may then stabilise, regardless of whether the patient's symptoms improve or not. Dermatological, endocrine and neurological manifestations of paraneoplastic syndromes are described in the articles that follow. In addition, cardiovascular, gastrointestinal, haematological, musculoskeletal and renal manifestations may occur.

Fever is the most common feature. Many clinical patterns may be observed, some of them simulating a common benign condition. When the underlying malignancy has not been found management is likely to be inappropriate.

Management

Treatment varies with the type and location of the paraneoplastic disorder. The therapeutic protocols are similar to neoplastic disorders without the presence of paraneoplastic syndrome. One therapeutic option is based on immunosuppression (by intravenous immunoglobulins, steroids, other immunosuppressive drugs, or by plasma exchange). This modality of treatment should be reserved for patients with clearly identifiable antibodies in their serum. If autoantibodies are detected, the best drug to use may be ciclosporin. Surgery, chemotherapy and radiotherapy are applicable to malignancies with or without paraneoplastic manifestations.

Because of their protean manifestations, paraneoplastic syndromes should be evaluated clinically by a team, including a medical oncologist, surgeon, radiation oncologist, endocrinologist, hematologist, neurologist and dermatologist.

Prevention

As with most cancers, no primary preventive measures are known for paraneoplastic syndromes.

Prognosis

The real incidence of deaths and serious complications related to paraneoplastic syndromes is unknown. Because paraneoplastic syndromes show wide individual to differences, prognosis may vary greatly. For example, disseminated intravascular coagulation (DIC) indicates a poor prognosis, whereas hypertrophic osteoarthropathy is one of the few paraneoplastic syndromes that may indicate a better prognosis.

Concluding remarks

Better comprehension of the molecular mechanisms of paraneoplastic syndromes will facilitate earlier diagnosis of cancer and assessment of the response to antineoplastic therapy, using cancer products as tumour markers.

Further reading

1. Paraneoplastic syndromes involving the nervous system. *New England Journal of Medicine* 2003; **349**: 1543-54.
2. Dalmau J, Rosenfeld MR. Paraneoplastic neurologic syndromes. In: Kasper DL, Bruanwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL eds. Harrison's Principles of Internal Medicine, 16th Edition, New York: McGraw, Hill 2005.

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