Asymptomatic peptic ulcer disease

Peptic ulcer disease is usually diagnosed on the basis of well recognised symptoms confirmed by endoscopy or barium study. Within the community an unknown number of people, however, may have peptic ulcer disease without symptoms, some of whom present only because of haemorrhage or perforation.[1] Roughly a third of the cases of perforated peptic ulcer, for example, occur in people without any previous symptoms, as do a fifth of gastrointestinal haemorrhage.[2,3]

There are no series reporting asymptomatic people who have been studied with endoscopy, and though necropsy studies indicate that almost a fifth of the population may have some evidence of peptic ulcer disease—active ulcer, scars, or previous surgery—the proportion of those without symptoms has not been recorded; nor is it clear whether the ulcer was a feature of the terminal illness.[4] Trials of treatment for duodenal and gastric ulcer have shown that ulcers may persist or recur in patients who have remained symptom free,[5,6] although they are clearly different from the general population in that they have previously had symptoms and will probably also develop further ones within the next year.[7] Elderly people, patients with rheumatoid arthritis, and those taking non-steroidal anti-inflammatory drugs are all at greater risk of peptic ulcer disease, which may remain asymptomatic until presentation with haemorrhage or perforation[8,9]; moreover, the non-steroidal drugs may also mask the symptoms of peptic ulcer.[10]

The prognosis for true asymptomatic peptic ulcer disease must be good as it will be discovered only at necropsy or not at all. Even if it is found apparently incidentally at endoscopy, however, it is difficult not to attribute some of the patient's vague gastrointestinal symptoms to the lesion. For patients with a perforated ulcer simple oversewing of the ulcer appears successful in that perforation recurs in only a few.[11] Although most of these patients remain symptom free, this does not imply that the ulcer has healed. Asymptomatic ulcer presenting with haemorrhage is a cause for concern, as the mortality may be high[3] and rebleeding may occur; long term medical treatment or close endoscopic surveillance is required.

Peptic ulcer represents a disease process continuing for perhaps 10-15 years,[12] and most patients are treated for their symptoms or given maintenance treatment for only a fraction of this time. For reasons of cost and feasibility—and often desirability—medicine today still responds only to the patient's symptoms and does little to offer surveillance to an asymptomatic person other than to one with a recognised increased risk of cancer. Hence, although a lot of people in the community are likely to have unrecognised peptic ulcer disease, any proposals for endoscopic or radiological screening to discover it, followed by treatment to suppress the process, are hardly likely to find favour with clinicians.

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Cutaneous graft versus host disease

Graft versus host disease occurs when immunocompetent lymphoid cells of the graft are introduced into an immunosuppressed histoincompatible host. In man it is seen most commonly as a complication of bone marrow transplantation. It may also occur after cell transfer from the mother to a fetus with cell mediated immunodeficiency and after transfusion of non-irradiated blood or blood products in immunodeficient patients. The skin is a major target organ of the disease and our understanding of the immunopathogenesis has important implications for dermatology. Cutaneous graft versus host disease provides a unique model for studying the pathogenesis of several "idiopathic" skin diseases.

In a study of 100 consecutive bone marrow transplantations performed at Westminster Hospital before 1983 the incidence of graft versus host disease was 76%, and in all cases the skin was affected.[1] Since then the routine use of cyclosporin A[2] and more recently T cell depletion of donor marrow[3,4] has greatly reduced the incidence. Skin manifestations are usually the earliest sign of the disease; in its acute form graft versus host disease is seen as a generalised morbilliform eruption with erythema of the palms and soles. The patients who are severely affected develop an exfoliative erythroderma which may progress to toxic epidermal necrolysis.[5] Chronic skin disease presents as a variety of lichenoid lesions[6] that are clinically and histologically indistinguishable from lichen planus followed by pigmentary changes, poikiloderma, and sclerosis (morphoea).[7-9] The last tends to be localised, although rarely it may become extensive (generalised morphoea). Oesophageal involvement and subcutaneous calcification, simulating scleroderma, have been reported.[10] Chronic graft versus host disease may also present as various autoimmune or connective tissue diseases, sharing overlapping features of lupus erythematosus, dermatomyositis, polymyositis, Sjögren's

syndrome, vitiligo, primary biliary cirrhosis, and chronic active hepatitis.[11]

In acute graft versus host disease mature T lymphocytes in the graft recognise the foreign antigens of the host, become activated, and then directly or through secondary mechanisms attack host cells. Although T lymphocytes are a necessary prerequisite for the acute disease, T lymphocyte cytotoxicity may not be the only effector mechanism. Sensitised T lymphocytes after interaction with host antigens release various lymphokines (interleukin 2, interferon, and so on) that may recruit and activate both donor and recipient mononuclear cells (macrophages, monocytes, or natural killer cells). Late manifestations of graft versus host disease are caused by the immunoaggression of donor lymphocytes derived from donor lymphoid stem cells that differentiate entirely within the recipient. The sclerotic change in the skin is probably related to the effect of lymphokines on collagen synthesis.[12,13]

Immunohistochemical studies of the skin in acute graft versus host disease have produced two important findings. Firstly, the Ia bearing epidermal dendritic (Langerhans) cells are appreciably reduced,[14] which cannot be explained simply by the effects of irradiation and chemotherapy alone,[15] suggesting that the Langerhans cell is the primary target in the skin. Delay in repopulation of Langerhans cells (donor derived) is influenced by the presence of continuing graft versus host disease.[16] Secondly, keratinocytes express Ia antigen during acute graft versus host disease[17,18] as well as in several other lymphocyte mediated skin diseases.[19] Keratinocyte Ia expression can be induced in vitro by γ interferon,[20] suggesting that during graft versus host disease sensitised T lymphocytes release lymphokines that induce the expression of Ia. The induced Ia could then become the target for T cell cytotoxicity.

The basis of acute graft versus host disease is the recognition of antigenic disparity between graft and host. The disease may occur, however, if the graft and host have identical HLA MLR matching, as in identical twins.[21] This implies that minor histoincompatibility differences are important, induced by viral infections, drugs, radiotherapy, or the primary disease itself. Viral infections, especially with cytomegalovirus, are common in patients undergoing bone marrow transplantation. Cells infected with a viral agent can induce neoantigens on their surface. The immune system may then recognise these cells as foreign and destroy them even when the infected cells and the immunologically competent donor cells have the same histocompatibility antigens.

What therefore can we learn from graft versus host disease? Maybe the disease is not just limited to bone marrow grafts but might develop in an individual in whom there has been an alteration of self antigens. This broader concept of graft versus host disease may help to advance our understanding of the pathogenesis of disorders such as lichen planus, toxic epidermal necrolysis, and morphoea. In addition, the knowledge gained from successfully preventing and treating graft versus host disease should improve our management of these conditions.

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