Recent advances in gastrointestinal lymphoma

P.G. Isaacson*

Significant advances in immunology and lymphocyte biology contributed to the emergence of the first rational classifications of the lymphomas in the early 1980s (1, 2). The emphasis of these classifications was to reconcile the properties of different categories of lymphoma with those of normal lymphoid cells and tissues. However, although differences between the peripheral and mucosal immune systems were beginning to receive attention (3), the possibility that there were differences between lymphomas arising in peripheral lymph nodes and those arising in extranodal sites, including the mucosa, was not considered. Gradually, significant clinical and biological differences between nodal and extranodal, principally gastrointestinal, lymphomas began to be recognised, and this has been partly responsible for the formulation of new lymphoma classifications (4). The incidence of specific types of lymphoma in the gastrointestinal tract and peripheral lymph nodes is strikingly different. Two of the commonest nodal lymphomas, namely Hodgkin’s disease and follicular lymphoma, only rarely occur as primary gastrointestinal tumours while certain other lymphomas are restricted to the gastrointestinal tract. Two gastrointestinal lymphomas that have evoked particular interest in this respect are gastric lymphoma of mucosa associated lymphoid tissue (MALT)-type (5) and small intestinal lymphoma that occurs in association with coeliac disease, so-called enteropathy associated T-cell lymphoma (EATL) (6).

The stomach is the commonest site of extranodal lymphoma and most cases are of MALT-type; that is to say that the histological features recapitulate those of Peyer’s patches. Recognition that gastric MALT lymphomas show evidence of immunological reactivity, coupled with the realisation that they arise from a background of MALT acquired as a consequence of Helicobacter pylori infection, led to experiments that showed that the growth of the lymphoma cells could be stimulated by co-culture with H. pylori (7). This in turn led to attempts to “cure” the lymphoma by eradication of H. pylori using antibiotics (8). Some 75% of these lymphomas regress completely after eradication of the organism (9) which raises some fundamental biological questions relating to the nature of malignancy. Current research is focussed on the genetic differences between antibiotic responsive and non-responsive gastric lymphomas particularly with respect to t(1;14)(p22;q14) and t(11;18)(q21;q21) translocations recently recognised as characteristic of MALT lymphomas (10, 11).

Observations made in 1978 showed that the small intestinal lymphoma that occurs in association with coeliac disease was a specific histological entity (12) and this was subsequently characterised as a T-cell lymphoma (EATL) (6). Later work suggested that EATL was derived from the intra-epithelial T-cell (IEL) population that is increased in coeliac disease (13). The onset of EATL is often preceded by loss of sensitivity to gluten withdrawal and, in some cases by the occurrence of small intestinal ulceration, so-called ulcerative jejunitis. Several groups have now showed that in this pre-lymphomatous phase of the disease, that may last months or many years, the intra-epithelial T-cells comprise a monoclonal population (14-17) that manifests the same immunophenotype as EATL. Moreover, it is this clone that expands to form the lymphoma. These findings have raised interesting questions regarding progression in lymphomagenesis and also thrown up therapeutic challenges relating to refractory coeliac disease which, in many cases, is evidently a monoclonal T-cell disorder.

The restriction of certain types of lymphoma to the gastrointestinal tract points to pathogenetic mechanisms, some of which involve infectious agents, that are different from those of nodal lymphomas. Further analysis of these mechanisms should provide insights into lymphoma biology that could be exploited therapeutically.

References