Immunosuppressive Therapy and Acquired Immunological Disorders

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Abstract

Impairment of the immune system by drugs, such as azathioprine and cyclosporin, or by diseases, such as AIDS, represents the most firmly established cause of non-Hodgkin's lymphoma (NHL). Neither drugs nor diseases, however, can explain the increases in the incidence of NHL in the general population, for these include cohorts relatively unexposed to immunosuppressive drugs or to AIDS. Furthermore, no immunological disorder that is associated with an increased risk of NHL is known to have increased in incidence. Among alternative explanations is the possibility of increased exposure to a lymphomagenic agent in the environment that acts by nonimmunological means. Pesticides and herbicides may belong to this category, but they will not explain the substantial increases in NHL in urban populations. However, the evidence of an underlying viral aetiology for the lymphomas in several different forms of immune impairment may be relevant to the increases in NHL in the general population. Paralytic poliomyelitis and mumps represent examples of diseases that have changed their pattern of occurrence in this century, consequent on changes in social conditions. It is therefore not impossible that changes in hygiene and in population density have altered the average age of exposure to a virus, thereby increasing the likelihood of a lymphomagenic effect.

Introduction

The most firmly established cause of NHL is immune impairment whether by drugs such as azathioprine or cyclosporin or by diseases such as AIDS. It is reasonable therefore to consider what implications this has, if any, for the increases reported in the general population.

Immunosuppressive Therapy

Transplant Patients. Cancer incidence in transplant patients on immunosuppressive therapy has, for obvious reasons, lent itself to more detailed epidemiological study than cancer in other states of immune impairment. A marked excess of NHL has been a consistent finding, though its magnitude has varied in different studies (Table 1) (1–3). However, the 46-fold increase found in a United Kingdom-Australasian study may be more accurate than the 26-fold increase found in a National Cancer Institute study (2), given the more even and complete nature of the follow-up. Those lymphomas associated with azathioprine showed a remarkable predilection for the brain, which was involved in almost half the cases.

The main factor that appears to influence the risk of NHL is intensity of the immunosuppressive therapy. Besides other evidence, this is reflected in the higher incidence in series of cardiac and pancreatic transplant patients who received an unusually intensive immunosuppressive regimen (1).

Patients without Transplants. Lymphomas were found to be increased 11-fold in patients without grafts who received immunosuppressive drugs (3). This suggests that the immunostimulation of foreign antigens in the graft is not crucial to the excess of lymphomas after organ transplantation, though it may contribute to the higher incidence in this group. None of the lymphomas in the nontransplant group involved the brain. Nevertheless, for so rare a malignancy, it is noteworthy that no less than 8 cases of cerebral lymphoma in such patients could be traced in the literature from the pre-AIDS era (3). It seems probable, therefore, that the above study (3) was not large enough to detect an excess.

Acquired Immunodeficiency Disorders

As others have pointed out in this workshop, AIDS involves both a severe immunodeficiency and an increased incidence of non-Hodgkin's lymphoma, often in the brain. Another common disorder involving a marked immunological abnormality is RA, and this also is associated with an excess of non-Hodgkin's lymphoma, even in the absence of azathioprine and cyclophosphamide. Since RA was well represented in the nontransplant group in the last-mentioned study (3), the role of immunosuppressive therapy in the excess of lymphoma might be questioned. In fact, the excess of NHL was broadly similar in those with and in those without RA (3). Moreover, it would be surprising if such treatment increased the incidence of NHL only in patients without RA and if a quite different cause explained the excess in rheumatoid patients following the same therapy. Nevertheless, some of the increase might well reflect the effects of the underlying disease. Details of cohort studies of cancer among rheumatoid patients not treated with azathioprine are shown in Table 2 (4–17). Not all of these studies presented details of the expected numbers of lymphomas and, when absent, these have been estimated by applying a conservative proportion to the total number of cancer deaths. In this way, an overall estimate of 2.5 was obtained for the relative risk of non-Hodgkin's lymphoma in patients with rheumatoid arthritis without azathioprine or cyclophosphamide. Table 3 shows corresponding details from studies of rheumatoid patients treated with azathioprine or cyclophosphamide. Overall there is a 10-fold increase of NHL in such patients (8, 18–23), 4 times greater than found in RA patients in the absence of such treatment. As none of these cohort studies were randomized trials, the possibility cannot be assessed of whether any of the excess of NHL shown in Table 3 reflects the effects of selection and disease severity. Nevertheless, these findings are consistent with the view that immunosuppressive agents such as azathioprine increase still further the elevated risk of NHL associated with rheumatoid arthritis, as suggested also in a study of Sjogren's syndrome (24). Here, immunosuppressive therapy was associated with a 100-fold increase of NHL compared with 35-fold in other patients (see Table 4).

Oncogenic Viruses

A striking feature of posttransplant lymphomas is the short interval after transplantation at which the excess is first evident, apparent after only 6 mo, less than the latent interval for any other known carcinogen. Indeed, it was this contrast that suggested more than a decade ago that the cause might differ fundamentally from that of most carcinogens, which are mainly...
chemical agents (1). In particular, the possibility of an oncogenic virus was raised. No malignancy is more linked with immunodeficiency than is non-Hodgkin's lymphoma, whether due to hereditary or acquired diseases or to medical treatment. Mounting evidence, and not only from posttransplant lymphomas, indicates an aetiological role for the Epstein-Barr virus in these situations (25, 26). This is in keeping with the evidence overall indicating that immunodeficiency is relevant primarily to malignancies of viral origin.

Implications

Does the above evidence concerning immune impairment provide any insights into the cause of the increases of NHL in the general population? It can be stated at once that neither immunosuppressive drugs nor AIDS can explain the increase, for crucial differences exist not only in the relevant calendar periods and geographical areas, but also in the sex and age groups of those mainly affected. However, I believe we can go further than this. It seems unlikely that the explanation can be the introduction into the environment of some unidentified immunosuppressive agent. All the immunodeficiency states known to be associated with increases of non-Hodgkin's lymphoma involve severe degrees of immunological impairment. Given that only a minority of patients with these states of immunodeficiency actually develop a lymphoma, then any disorder postulated as underlying the general increases of NHL would itself have to be relatively common and also to have increased markedly over recent decades. No such clinical disorder is known. This argument leaves open the possibility of an increased prevalence of some agent in the environment capable of causing NHL by other means than those discussed above. Only for pesticides and herbicides is there such evidence, but these can hardly explain the major increases of lymphomas in urban populations.

However, a quite different type of cause may deserve consideration, namely, one involving change, not in the “seed,” but in the “soil.” Thus, if no limit be set on speculating about possible recent immunological changes, then it may be observed that the calendar period of the lymphoma increases covers the first period in mankind's history in which the immune system has had “assistance” in combating infections from antibiotics. However, if we discount this possibility (I know of no evidence that would support or refute it), there is, I consider, a more plausible hypothesis of this general type.

A widespread virus is involved in the causation of lymphomas in such special groups as transplant patients, then it is reasonable to consider a similar aetiology (though not necessarily Epstein-Barr virus) for the increases in the general population. This possibility does not require postulating the introduction of a new virus into human populations, or even an increased prevalence of any existing agent. For we have in mumps and paralytic poliomyelitis examples of illnesses that have changed their pattern of occurrence during this century, consequent on changes in social conditions. Similarly, it may not be impossible that changes in hygiene and in the density of human populations have altered, for example, the average age of a community's exposure to some virus so that, in turn, the likelihood of an oncogenic effect is increased.

References

2. Hoover, R. N.; and Fraumeni, J. F. quoted in Ref. 1 above.
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