CORRESPONDENCE

Integrating the Time Factor Into the Definition of Metastasis of Unknown Origin

Patients with cancer of unknown primary site are common, representing 5%-10% of all cancer patients (1). Combination chemotherapy, often used with surgery or radiation therapy, has proved to be potentially curative for several metastatic tumors of known primary site. Likewise, some patients with metastasis of unknown origin (MUO) also have responsive neoplasms and could be treated successfully (2,3). There is no doubt that, unless the primary tumor is promptly diagnosed and treated, most of these cases will have a rapid downhill course. Therefore, time is also an important factor in the work-up and management of these patients.

In infectious diseases, fever of unknown origin (FUO) is defined as an illness of more than 3 weeks’ duration, documented fevers above 38.3 °C (101 °F) on several occasions, and the lack of a specific diagnosis after 1 week of inpatient investigation (4). This definition has been updated by Petersdorf (5) who suggested “One week of intelligent and intensive investigation, which, in most patients, could be conducted on an outpatient basis. However, a minimum temperature of 38.3 °C and 3 weeks of fever is necessary for the diagnosis of FUO.”

Most physicians send the patients with cancer of unknown primary site to the major referral centers with diagnostic and therapeutic facilities. Unlike the diagnostic procedures in infectious diseases, the work-up in oncology patients is somewhat more complicated and time consuming. We propose that the time factor should also be integrated into the definition of MUO. Accordingly, MUO may be defined as the presence of metastatic illness with an unknown primary site after 2 weeks of intensive investigation at a center with good diagnostic facilities. Those who deal with cancer should never forget that the elapsed time without diagnosis and delay in therapy may worsen the prognosis in these patients.

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Note

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Re: Lung Cancer After Hodgkin’s Disease

Travis et al. (1) reported increased lung cancer occurrence following Hodgkin’s disease (HD). Initial radiotherapy and chemotherapy are definitely likely candidates for an etiologic role. However, as they correctly pointed out, the significant excesses observed within 5 years after therapy do not seem to be consistent with the current understanding of latency periods for radiation-induced lung cancer. Also, although not statistically significant, possibly because of small numbers, increased risks of lung cancer within 9 years of diagnosis of HD were seen in subjects with HD who did not receive radiotherapy and chemotherapy; no excess risk was apparent in this group at 10 or more years after diagnosis. Finally, the overall risk of 3.03 in subjects with HD who received both radiotherapy and chemotherapy was virtually identical to that of 3.09 for those who received radiotherapy alone. Taking these observations together, an alternative explanation could be that the association between HD and lung cancer may result from both conditions being caused by the same etiologic agent, with lung cancer occurring later because of longer latency.

There is substantial evidence of excess lung cancer among meatworkers, particularly those involved in slaughtering animals for food consumption who are potentially exposed to the oncogenic viruses of cattle and chickens (2,3) [see also references cited in (3)]. Among the studies cited in reference (3) are the only three cohort studies that also provided information on lung cancer and HD. In one of these cohorts, a statistically significant proportional mortality ratio of 2.9 and a nonsignificant standardized mortality ratio of 2.2 for HD were observed on the basis of only four deaths. Despite the small numbers, a clear dose–response relationship was observed. There was additional evidence that the risk was highest in small abattoirs where only killing was carried out (4). In this same cohort, a very high risk of lung cancer has also been observed associated with killing (2). The other two cohort studies (5,6) also reported a statistically significant excess of lung cancer and twofold nonstatistically significant standardized mortality ratios for HD. This seeming consistency across these studies originating from widely differing populations in three different countries may suggest that these findings may be of significance. This is offered as a possible example that the association of lung cancer in patients with HD may be due to a shared etiologic agent, which could also interact with radiation therapy and chemotherapeutic agents in giving rise to lung cancer in these patients with HD.