AL AMYLOIDOSIS

The committee has moved the section on AL amyloidosis from its position in previous VAO updates, where it was grouped with a variety of non-neoplastic health conditions, to put it closer to related conditions, such as multiple myeloma and some types of B-cell lymphoma. The conditions share several biologic features, most notably clonal hyperproliferation of B-cell-derived plasma cells and production of abnormal amounts of immunoglobulins.

The primary feature of amyloidosis (ICD-9 277.3) is the accumulation and deposition in various tissues of insoluble protein, historically termed amyloid. A wide spectrum of disease can stem from this; excessive amyloid protein can have limited clinical consequences or can produce severe, rapidly progressive multiple-organ-system dysfunction. Annual incidence is estimated at 1/100,000; there are about 2,000 new cases each year in the United States. Amyloidosis occurs mainly in people 50–70 years old and occurs more often in men than in women (Solomon, 1999).

Amyloid protein accumulates in the extracellular spaces of various tissues, often affecting multiple organ systems. The pattern of organ involvement depends on the nature of the protein; some amyloid proteins are more fibrillogenic than others. Amyloidosis is classified according to the biochemical properties of the fibril-forming protein, with the letter A (for amyloid) as the first designation. AL amyloidosis is the most common form of amyloidosis; the L indicates that the amyloid protein is derived from immunoglobulin light chains. That links AL amyloidosis with other B-cell disorders that involve overproduction of immunoglobulin, such as multiple myeloma and some types of B-cell lymphomas.

AL amyloidosis results from the abnormal overproduction of immunoglobulin light chain protein from a monoclonal population of plasma cells. Clinical findings can include excessive AL protein or immunoglobulin fragments in the urine or serum, renal failure with nephrotic syndrome, liver failure with hepatomegaly, heart failure with cardiomegaly, marcglossia, carpal tunnel syndrome, and peripheral neuropathy. Bone marrow biopsies commonly show an increased density of plasma cells, suggesting a premalignant state. Historically, that test emphasized routine histochemical analysis, but modern immunocytochemistry and flow cytometry now commonly identify monoclonal populations of plasma cells with molecular techniques. AL amyloidosis can progress rapidly and is often far advanced by the time it is diagnosed (Buxbaum, 2004).

Conclusions from VAO and Updates

The VA identified AL amyloidosis as of concern after the publication of Update 1998. AL amyloidosis was considered by the committees responsible for Update 2000, Update 2002, and Update 2004. Those committees concluded that there was inadequate or insufficient evidence to determine whether there is an association between exposure to the compounds of interest and AL amyloidosis.

Update of the Epidemiologic Literature

Because it is a rare condition, there is little epidemiologic literature specifically on AL amyloidosis. Cohen et al. (2004) describe a series of six patients with AL amyloidosis in association with NHL; risk
could not be estimated, because the study design did not include a control group for comparison, but the report indicates that the two conditions are closely related.

Rajkumar et al. (2006) review the relationship between AL amyloidosis and other plasma cell disorders. They describe AL amyloidosis as a clonal plasma cell disorder characterized by low tumor burden but profound multisystemic disease. No new occupational, environmental, or Vietnam-veteran studies concerning exposure to the compounds of interest and amyloidosis of any sort were published since Update 2004.

Biologic Plausibility

A 1979 study reported AL amyloidosis in association with chronic skin lesions in Swiss mice after chronic exposure to TCDD (Toth et al., 1979). That finding has not been reported in later studies of TCDD carcinogenicity in mice or rats. The observation of common chromosomal abnormalities in AL amyloidosis and multiple myeloma (Harrison et al., 2002) and of “progression” from AL amyloidosis to multiple myeloma (Rajkumar et al., 1998) support the biologic plausibility of linking AL amyloidosis with multiple myeloma.

It is known that AL amyloidosis is associated with B-cell diseases and roughly 15–20 percent of the time it occurs with multiple myeloma. Other diagnoses associated with AL amyloidosis include B-cell lymphomas (Cohen et al., 2004), monoclonal gammopathies, agammaglobulinemia, and monoclonal gammopathy of undetermined significance (Rajkumar et al., 2006). Thus, AL amyloidosis can result from such medical conditions as multiple myeloma and B-cell lymphomas for which there is evidence of association with exposure to the compounds of interest.

Synthesis

AL amyloidosis is a very rare condition, and it is not likely that population-based epidemiology will ever provide substantial direct evidence regarding its causation. However, the biologic and pathophysiologic features linking AL amyloidosis, multiple myeloma, and some types of B-cell lymphomas—most notably clonal hyperproliferation of plasma cells and abnormal immunoglobulin production—indicate that AL amyloidosis is pathophysiologically related to those conditions.

Conclusion

On the basis of its evaluation of the evidence reviewed here and in previous VAO reports, the committee concludes that there is limited or suggestive evidence of an association between exposure to the compounds of interest and AL amyloidosis.