Fever of Unknown Origin: A Changing Diagnostic Spectrum

Fever of unknown origin (FUO) had remained a poorly-defined clinical problem until the 1961 publication of Petersdorf and Beeson proposing specific criteria for FUO (1). Their criteria for FUO included 3 conditions: 1) illness of more than 3 weeks’ duration, 2) documented fever higher than 101°F (38.3°C) on several occasions, and 3) uncertain diagnosis after 1 week of hospitalized investigation. The proposal of the new criteria was timely and quickly this became the paradigmatic criteria for FUO.

Since the original 1961 report which was based on clinical materials gathered between 1952–1957, it soon became apparent that the diagnostic spectrum of FUO was changing over time (2). For instance, certain diseases like rheumatic fever had become less frequent, while diseases like lymphoma had increased considerably. Factors responsible for this change are complex. Improvements in socioeconomic status and advances in diagnostic medicine and therapeutic practice are but a few examples of factors which have influenced the diagnostic spectrum of FUO. Elsewhere in this issue of Internal Medicine, two groups of investigators report their latest findings on FUO (3, 4).

Iikuni and colleagues analyzed 153 patients with FUO seen at their university hospital between 1982 and 1992 (3). In comparison with their earlier report published in 1983 (5), they found an increase in collagen-vascular disease and a corresponding decrease in infection. Among the collagen-vascular diseases, adult Still’s disease and vasculitis syndrome were dominant. Because of the rapidly growing proportion of the elderly population in our community, it is no wonder that more patients with FUO are ultimately diagnosed as having polymyalgia rheumatica or polyarteritis.

The formidable spread of human immunodeficiency virus (HIV) infection over the past decade has changed the classic concept of FUO in many countries where it is not uncommon. Fortunately, at this time, HIV infection in Japan appears to be still relatively rare, but the situation may change in the near future. Although Iikuni and colleagues did not include an HIV antibody test in their study, any future studies of FUO must include this test.

The health environment and medicine have undergone revolutionary changes during the past 3 decades. Disease statistics have sensitively reflected these changes, and the diagnostic spectrum of FUO is no exception. I believe the 2 articles on FUO in this issue of the Journal exemplify some of the important changes which are taking place today.

In our analysis of 56 patients with FUO assembled between 1976–1985, we pointed out that patients with FUO with the ultimate diagnosis of malignancy required a shorter period of investigation than patients with other major categories such as infection and collagen-vascular disease (6). We then assumed that prompt identification of space-occupying lesions by modern devices and an equally prompt use of biopsy were contributory to this efficiency. Likewise, in their update study of FUO, Knockaert and his Belgian coworkers pointed out that tumors were a less important cause [7%] of FUO (7). They suspected that the widespread use of ultrasonography and CT helped clinicians to discover solid tumors more easily which otherwise would have escaped early detection. According to the report by Shoji et al malignancy accounted for 9% of the total, a figure consistent with the most recently reported trend (4). In this context, it is somewhat puzzling to find that the incidence of malignancy as reported by Iikuni and colleagues remained identical in their 2 series of patient information collected over the periods of 1971–1982 and 1982–1992.

Shoji and coworkers analyzed 80 patients with FUO seen by internists in the Shin’etsu area, in the center of Japan’s Honshu Island (4). As these patients were assembled from 10 mostly non-university hospitals distributed over 2 prefectures, Nagano and Niigata, the study obviously suffers from the heterogeneity of human resources and medical facilities. Despite these drawbacks, this brief report seems to throw a sidelight on the recent trend of the diagnostic spectrum of FUO. The fact that the number of patients with malignancy was small has been already mentioned. The study also underlined that adult Still’s disease was important in the collagen-vascular disease category.

Adult Still’s disease is a systemic inflammatory disease of unknown etiology characterized by fever, arthralgia and/or arthritis, an accelerated erythrocyte sedimentation rate and leukocytosis (8). As a rule, rheumatoid factor and antinuclear antibodies are negative. Fever is characteristically a highly remittent or intermittent pattern. Maculopapular skin rash is of diagnostic help. There is no laboratory test specific for this disease, but the presence of a very high serum ferritin is considered highly suggestive for diagnosis. The diagnosis is usually made by exclusion and the overall clinical picture. Although considered relatively rare in Japan until recently, Ohta, Yamaguchi and coworkers were able to assemble 90 patients with the typical clinical picture of adult Still’s disease from a multicenter survey in 1990 (9).

The study by Shoji et al also revealed a strikingly high proportion of patients (54%) with infection. As the patients in this study were distributed over areas with less urban conditions, the figures may reflect the true preponderance of infection among FUO in the communities of these areas. I suspect, however, a part of this exaggeration is due to the inclusion of inflammatory diseases of uncertain etiology such as interstitial
pneumonitis and subacute necrotizing lymphadenitis in the infection category.

The present criteria for FUO was proposed more than 30 years ago. There are arguments that the criteria should be revised to meet the changing face of medicine (7, 10). Whatever the modification, one must especially bear in mind that the revised criteria should be the product of the concerted efforts and opinions of expert internists in FUO. Otherwise, we may only help reshape FUO into a poorly-defined monster again.

Heihachiro KASHIWAGI, M.D.
Professor of Internal Medicine,
Institute of Clinical Medicine,
University of Tsukuba,
Tsukuba-shi, Ibaraki 305

References