Periodic (Pel-Ebstein) Fever of Lymphomas

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ABSTRACT

During lymphomatous diseases, bouts of intermittent or relapsing Pel-Ebstein fever occasionally repeat in remarkably regular tempo resembling the episodes of benign periodic fever. Febrile episodes alone, especially during acute lymphomatous disease, occasionally precede overt evidence of underlying disease for months. In that event, diagnosis and treatment of lymphomas are delayed. Regular febrile bouts are either uniquely characteristic of lymphomas or represent the imposition of periodic fever. Apprehension of malignant disease during benign periodic fever may induce intensive investigation. Malignant disease has not ensued in reported cases of periodic fever.

Fever during lymphomatous diseases has posed problems for more than a century. Whether fever is of infectious origin or a part of the diseases assumed more importance after the use of antimicrobial and immnosuppressive therapy began. Longer survival now and host-resistance unavoidably impaired by therapy have complicated the problem and increased the incidence of opportunistic infections. This essay pertains to the remarkable temporal precision or near precision of recurrent febrile episodes, known as Pel-Ebstein fever in lymphomatous diseases, and its counterpart in benign periodic disturbances.

Relapsing fever with transient swelling of lymph nodes and spleen were first noted by Hodgkin himself in 1832,12 then by Murchison in 187016 and by Gowers in 1879.10 Six years later, Pel regarded the condition as an infectious form of pseudo-leukemia.17 Ebstein in 1887 mistook the febrile bouts for evidence of a new infectious disease.9 Despite the lapse of time, priority and error, the term Pel-Ebstein fever became widely accepted.

In 1938, Ask-Upmark chose the preferable descriptive term periodic fever instead.2 His monograph has 240 references to pertinent articles mostly in European journals, a detailed discussion and many charts depicting periodic febrile episodes in Hodgkin disease, lymphosarcoma, leukemia and others.

Typical Pel-Ebstein fever appeared in 5% to 15% percent of cases of febrile Hodgkin disease, in 0.5% to 13% percent of lymphatic leukemias, and during lymphosarcoma.24 For a century the surprisingly predictable regular tempo of febrile episodes has attracted little attention. Strict periodicity may be obscured by fluctuations in the course of the diseases, by intercurrent infection and by modern therapy. Febrile periodicity per-
sisted during therapy in some patients with Hodgkin disease and with lymphosarcoma.2

The Episodes

Febrile episodes last several days and come at intervals of about, or precisely, 7, 14, 21 and 28 days alternant with days of normal temperature as exemplified in the figures. In some instances, fever tracings are wavy, seldom touching 37°. In others, the charted course of intermittent fever looks butte- or mesa-like. In many patients, lymph node swelling or splenomegaly or both, if present in the early stage, enlarge during each episode then subside. Spontaneous termination of episodes may be misascribed to antimicrobial therapy. In some instances, febrile episodes alone, with relief from symptoms in the interims, antedate overt evidence of underlying lymphomatous diseases by weeks or months delaying diagnosis and therapy.

Febrile bouts tend to lengthen, intensify and often are terminal; otherwise they are identical in duration and tempo to those of the entity periodic fever.22 During benign periodic fever, the apprehension of latent fatal disease may entail much diagnostic effort until underlying disease is reasonably excluded. Febrile bouts of periodic fever recur quite uniformly for decades. Thus far among 70 cases,21 lymphomas have not been present or have not yet been reported.

Illustrative Cases

Case 1. Murchison's patient, a child with "lymphadenoma" had 10-day bouts of fever recurrent every four weeks. Nodes in the axillas and groins enlarged during each episode. Necropsy at two years after the onset disclosed an enlarged spleen, liver and internal lymph nodes.16

Case 2. Ebstein's 19-year old patient had undulating fever lasting eight to 14 days and recurrent at 21-day intervals as recorded during 211 days (figure 1). The spleen was palpable and the blood count was normal.9 Pel questioned the diagnosis of chronic relapsing fever because necropsy later disclosed an enlarged spleen, liver and mesenteric lymph nodes.17,18

Batty Shaw reviewed 17 cases of lymphoma with relapsing fever and introduced the term "periodic fever" in 1901.5

Case 3. One of MacNalty's patients, aged 17, had occasional episodes of fever without lymphadenopathy or splenomegaly six weeks before observation in a hospital. Several weeks later, the cervical and axillary nodes enlarged at seven day intervals, but only during the fever (figure 2). Biopsy of a node disclosed lymphoma. Subsequent episodes intensified and lengthened to 10 to 15 days before the patient left the hospital. Twenty-seven similar cases described by others were cited.13

Case 4. Barron's patient, aged 42, with known Hodgkin disease had seven-day fever in a rhythm of "exactly three weeks from onsets to onsets." Each bout worsened during eight months until death during the predicted twelfth episode.4

Five reports from France described relapsing fever suspected as of infectious origin in adults 25 to 36 years old.1,7,8,14,15
In four of them, episodes came at regular intervals of 14 days (bimensuelle) as shown in figure 3 and in one, every 21 days. Charted febrile bouts in one case appeared butte- or mesa-like (figure 4); in another, fever undulated in the same tempo (figure 5). In each patient, the severity of symptoms increased during four months to a year before diagnosis of "malignant reticulose" was made by biopsy or at necropsy.

SARCOMA

Renver's patient, aged 31, was thought to have lead poisoning or typhoid because of fever, colic, leukopenia and splenomegaly. During three months, the spleen enlarged. Anemia, weight loss and deterioration ended in death seven months after the onset. Five observed episodes of fever each lasting about seven days occurred at predictable 14-day intervals. Episodes in Völkers' patient came every 21 days. Three of Ask-Upmark's patients, aged 13, 26 and 28 years, had osseal sarcoma and febrile episodes "almost every week" undisturbed by radiotherapy (charts 2, 3, 4).

Harada's 28-year old Japanese patient had febrile bouts alone at precise seven-day intervals "on Saturdays and Sundays" (figure 6). After five months of observation, laparotomy disclosed reticulum-cell sarcoma of the mesenteric lymph nodes.

In one patient with Hodgkin disease, febrile episodes and "periodical hemolytic anemia" coincided. In another, severe lymphocytopenia accompanied febrile episodes at five to 10 day intervals.

CASES OF SUSPECTED LYMPHOMA

Case 5. Because of fever recurrent about every 21 days, Hodgkin's disease had been suspected for eight years in an otherwise healthy man. Many tests, biopsies and a laparotomy all yielded normal findings. Febrile episodes lasting four to five days still repeat every 20 to 23 days after 12 years without evidence of other disease. Periodic fever was diagnosed.

Case 6. Febrile episodes with chills and vomiting began in a 42-year old man. Similar ones lasted four days, then recurred regularly every 24 days. During eight months of observation, episodes intensified with severe disabling illness of 12 to 14 days every four weeks and progressive loss of weight and anemia. No adenopathy or splenomegaly appeared. All thoracic and osseal roentgenograms were normal. Albuminuria and leukopenia were noted. Bilirubinemia and bromsulfalein retention, only during the episodes, indicated hepatic disturbance. Hodgkin disease was suspected. The patient died a year after the onset.

Discussion

Periodic fever recurring at fairly regular or precise intervals occasionally accompanies or terminates lymphomatous diseases. The curious rhythm is attested
by many records since Hodgkin's and Murchison's reports, MacNalty's and Batty Shaw's reviews, Ask-Upmark's monograph and by the data recorded here.

Recurrent bouts of fever with minor symptoms for weeks or months usually are mistaken for evidence of infection. As a rule, the duration and severity of episodes worsens. Finally, lymphadenopathy, splenomegaly, progressive anemia and deterioration lead to biopsy, laparotomy or necropsy and correct diagnosis. All patients cited were less than 46 years old and the disease seldom lasted more than a year. In contrast, similar episodes of benign, hereditary, periodic fever recur for decades with good health otherwise, and in some instances cease spontaneously.22

PERIODICITY

The unique pattern of precise, or fairly precise, febrile bouts recurrent about every seven or multiples of seven days during lymphomatous diseases generally escapes attention. It becomes obvious when episodes are plotted graphically as in the figures. Among the cases cited, fever recurred about or exactly every seven days in five cases, every 14 days in five cases, every 21 days in six cases and every 28 days in two cases.

Noteworthy is the striking similarity of figure 7 to Richter's figures 18 and 20 of periodic fever with regard to the tempos just mentioned. Perhaps the periodic fever of lymphomas, the episodes of benign periodic fever and the 23 to 33 day fluctuations of human behavior arise from the same rhythmic stimulus.

Ask-Upmark ascribed febrile periodicity to repetitive excitation of the hypothalamus or of the reticuloendothelial system.2 Question arises if periodic fever as such is superimposed during lymphomatous diseases or if repetitious fever is characteristic of them.

Of added interest are reports of 12 patients with periodic neutropenia and thrombocytopenia during leukemia.26 Episodes recurred in regular tempos averaging 35 days. They are longer than those of periodic fever and of the 21-day periodic neutropenia in otherwise healthy patients.21

Theoretically, an inherent biorhythm or a feed-back mechanism excites the
hypothalamus at intervals and the effects are mediated autonomically to genetically sensitive tissues. Why periodic events characterize some cases of lymphomatous diseases is unknown.

References