LEUKERGY - A NEW DIAGNOSTIC TEST FOR BONE INFECTION

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This new blood test for infection is based on the phenomenon of leukergy in which white cells agglomerate in the peripheral blood of patients with inflammatory diseases. It was used in 26 patients with proven bone or joint infection and was positive in 25. The leukergy test was more accurate than the ESR, white cell count or blood culture. The percentage of cells agglomerated correlated with the clinical severity of the infection and the test detected reactivation of the septic process better than the other haematological tests. It is a rapid and inexpensive method which is useful in the diagnosis and management of bone and joint infections.

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The prompt diagnosis of bone infection is important in order that appropriate treatment can be started as soon as possible. Acute infections with overt signs of inflammation, sinus formation and systemic illness are relatively easy to diagnose but low-grade infections are more difficult. Persistent elevation of the ESR suggests infection but is neither very sensitive nor specific (Carlsson 1978; Sanzén and Carlsson 1989). The results are better if the ESR is considered in conjunction with measurement of the C-reactive protein level but even then it is generally unreliable (Sanzén and Carlsson 1989). A low level of lactic acid in the fluid aspirated from a joint reliably excludes infection but an elevated level is not diagnostic (Curtis, Newman and Slack 1983; Newman, Curtis and Slack 1983). Radiographs may be difficult to interpret especially in the presence of an implant, isotope scanning is sensitive but not specific, and labelled white cell scanning gives a high incidence of false-positive results.

Leukergy is the phenomenon in which white blood cells agglomerate in the peripheral venous blood. It was first identified by Fleck in 1956 and has been shown to occur in several metabolic disorders including those associated with burns, acute pancreatitis and some other non-infectious inflammatory conditions. Furthermore, the degree of leukergy has been shown to correlate with the activity of these disease processes (Berliner et al 1985).

We report the first use of the measurement of leukergy in the early diagnosis and monitoring of bone sepsis.

PATIENTS AND METHODS

We studied 26 consecutive patients who were either known to have osteomyelitis or in whom the diagnosis was subsequently confirmed bacteriologically. Their mean age was 53 years (19 to 83) and the male to female ratio was 3:1. All were treated with antibiotics. Table 1 gives their clinical details.

The severity of the infection was graded clinically as follows: grade 0, no local or systemic signs of disease; grade 1, mild local pain without pus formation and no systemic signs; grade 2, moderate local pain with pus formation and no systemic signs; and grade 3, severe local pain and pus formation associated with pyrexia and other systemic signs of sepsis.

Leukergy testing was performed weekly on venous blood samples using the authors’ modification of the technique of Fleck (1956). Venous blood (1 ml) was mixed with 3.8% sodium citrate (4 ml) and a drop of the mixture was placed on a slanted microscope slide and dried. Erythrocyte haemolysis was achieved by repeated freezing and thawing of the blood sample and fixation was performed with methanol, followed by staining with nuclear fast red. On each slide three microscope fields of 300 white cells of all types were counted and the percentage of leukergy (agglomerated cells) was calculated. Agglomeration was considered to be positive when
at least three leukocytes were in close proximity, the distance between their nuclei being less than the diameter of one cell (Fig. 1). The count was made twice and the final leukergy result was the average of the two readings. At the time that blood was drawn for the leukergy test, samples were also taken for the measurement of the white cell count (Coulter counter), ESR (Westergren) and blood culture.

As a control group we used 20 age- and sex-matched healthy volunteers with no evidence of sepsis.

**Statistical analysis.** The statistical correlations between the clinical grading of the infection and leukergy, the white cell count and the ESR were tested by the Spearman rank test and the Pearson test.

**RESULTS**

The leukergy result was graded from 0 to 3 according to the percentage of aggregated cells: 0 = < 10%; 1 = 11% to 19%; 2 = 20% to 34%; and 3 = > 35%. The mean result for the control group was 7.2% with all results less than 9% (grade 0). In 25 of the 26 patients the leukergy value was significantly elevated before treatment was started. Its level correlated better with the clinical grade of disease severity than did the other haematological tests (Tables II and III). The latter showed the same trends of elevation to match the severity of clinical disease but they did not achieve similar levels of statistical significance. Furthermore, in the six patients with minimal clinical signs (grade 1) the leukergy value was significantly elevated although the ESR and white cell count were both within the normal ranges. These six patients all deteriorated...
over the next four to six days and their clinical signs became more obvious.

After treatment, the leukergy value was the last to return to normal in all patients.

In 15 patients antibiotic treatment was discontinued when the leukergy value returned to normal; none had subsequent recurrence of the sepsis. Antibiotic treatment was stopped in ten patients when all the other tests had returned to normal although the leukergy value had remained raised; in three of these cases reactivation of the septic process occurred.

In five patients the leukergy test failed to show any decline towards normal levels as treatment progressed, even although the bacteria isolated were shown to be sensitive in vitro to the antibiotic prescribed. In these patients the antibiotic was changed, resulting in clinical improvement followed by subsequent reduction of the leukergy values to normal.

DISCUSSION

This study has shown that the quantitative assessment of leukergy in the peripheral venous blood is a useful test for the diagnosis of bone sepsis and for monitoring the infective process during therapy. Leukergy was found to be more sensitive than the white cell count or the ESR. In the 26 patients it correctly detected 25 cases of infection whereas the white cell count and the ESR identified only 15. Leukergy was also more reliable in detecting the eradication of infection. Occasionally, it was found to forewarn of an impending deterioration before the appearance of clinical signs and to indicate the necessity for continued antibiotic treatment. It proved to be a reliable indicator of disease activity even when other laboratory tests were normal.

Previous attempts to develop a serological technique for the reliable diagnosis of bone infection have resulted in complicated tests requiring special equipment. They have proved expensive and unreliable (Krieker and Lambert 1992). The measurement of leukergy has been shown to be a simple, rapid and inexpensive technique requiring no special equipment.

In this study we did not explore the mechanism of leukergy but only documented its relationship to bone sepsis. The phenomenon probably results from cellular rather than humoral activity since it does not occur when leukocytes from normal individuals are placed in plasma taken from patients in whom agglomeration has been observed. Recent studies suggest that circulating mediators released during bacteraemia may lead to increased sensitivity of neutrophil adhesive receptors (Smith et al 1989; Walsh et al 1991).

The leukergy test may be valuable in distinguishing septic from mechanical loosening of prostheses and we are currently investigating its use in such cases.

It should be emphasised, however, that the leukergy result must be interpreted with caution since its level may be raised in some non-infectious conditions such as polycythaemia rubra vera (Fischer 1985), ischaemic heart diseases (Berliner et al 1986) and some rheumatic diseases (Berliner et al 1985).

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