Gross synovial fluid analysis in the differential diagnosis of joint effusion

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Aims: To develop an objective and easy to complete standardised questionnaire for documentation of synovial fluid (SF) gross appearance and use it in the assessment of patients presenting to the rheumatology service with a joint effusion.

Methods: A standardised questionnaire to record the gross appearance of SF was developed. Interobserver error in recorded observations and direct gross analysis of synovial fluid between four observers was calculated in a pilot study. In a prospective study over 8 months, SF gross analysis and cell count were documented in all patients presenting with a joint effusion. Fusch Rosenthal manual counting chamber was used for calculating SF cell counts.

Results: There was good interobserver agreement on direct gross analysis and between questionnaire assessors (mean κ 0.889). 80 SF samples were collected. Gross analysis was performed in all samples and cell count in 72. Of the specimens thought to be inflammatory on gross analysis, 31% were found to be non-inflammatory based on cell count; however, 12 of these patients had an established inflammatory arthritis. Gross analysis had a sensitivity of 94% and specificity of 58% when used to determine whether SF is inflammatory or non-inflammatory. The positive and negative predictive values were 0.69 and 0.91 respectively.

Conclusions: SF cell count did not add any information when SF gross analysis suggested a non-inflammatory process. Gross analysis was better than cell count to determine a potentially septic joint fluid. Further work needs to be done on the value of SF cell counts if gross analysis suggests the fluid to be inflammatory.

Synovial fluid (SF) analysis has been widely recommended as a crucial aid in the evaluation of patients with arthritis and joint effusions.^{1–5} The British Society for Rheumatology (BSR) and American College of Rheumatology (ACR) have published guidelines for analysing SF on patients presenting with joint effusions, which include:

- Gross analysis (viscosity, colour and clarity).
- Cell count.
- Polarised light microscopy (PLM).
- Microscopy and culture.^{6,7}

Gross analysis in particular is a simple bedside test, but is often poorly performed and documented by medical staff.

A recent postal survey has shown that the use of cell counts is not widespread and the methods used for performing cell counts and interpretation of results are not standardised.⁸ Consequently rheumatologists and orthopaedic surgeons have low confidence in the results generated.

This study aimed to evaluate these current guidelines on SF analysis and its relevance to clinical practice.

METHODS

Study design

A prospective study was undertaken in a district general hospital serving a population of 205 000 between March and October 2003. All adult patients (>16 years of age) presenting with a joint effusion were included in the study. This included patients seen in outpatient clinics or referred from accident & emergency, medical and other specialties within the hospital. Three consultant rheumatologists and two middle grades participated in the study.

Development of standardised questionnaire for recording SF gross analysis

A standardised questionnaire was developed to analyse and record the gross appearance of SF according to BSR and ACR guidelines^{6,7} (fig 1).

In a pilot study, completion of the questionnaire was tested on SF samples that were each examined by two independent observers. One of the observers was blinded to the patient's clinical details. Differences in the scoring and the conclusion of each observer were noted. Interpretation of the questionnaire results without an opportunity to directly examine the synovial fluid was also assessed in four independent observers. Interobserver agreement in this latter task was assessed using κ scores.

Patient demographics

All patients were assessed by any of the five participating physicians. Patient demographics, known rheumatological diagnosis, local examination findings, laboratory results, any joint x ray results, details of disease modifying antirheumatic drugs (DMARDs) and previous intra-articular steroid injections were recorded on standardised forms by the assessing physician.

Gross SF analysis

The questionnaire was used to analyse and record the gross appearance of SF in the prospective study by the assessing physician after joint aspiration. A decision was made as to whether the fluid was non-inflammatory, inflammatory or potentially septic.

Abbreviations: ACR, American College of Rheumatology; BSR, British Society for Rheumatology; DMARD, disease modifying antirheumatic drug; PLM, polarised light microscopy; SF, synovial fluid

Clarity (newsprint test)	
Transparent ☐	Translucent ☐ Opaque ☐
Viscosity (string test)	
String only ☐	String and drops ☐ Drops only ☐
Colour	
Colourless/straw coloured	☐
Yellow/green	☐
White/cream/brown	☐
Blood stained	☐
Haemorrhagic	☐

Figure 1 Standardised questionnaire with tick box system to analyse and document gross appearance of synovial fluid.

Cell count analysis

SF samples were transported to the laboratory in universal containers and examined on the same day. Cell counts were performed using the Fusch Rosenthal chamber via the standard manual technique by the microbiology technicians. The following reference ranges were used to differentiate between the three categories.^{3 5 9 10}

- Non-inflammatory: <2000 cells/mm³
- Inflammatory: 2000–50 000 cells/mm³
- Potentially septic: >50 000 cells/mm³

PLM and microbiological assays were performed where clinically indicated. A final diagnosis was then established for each patient from case sheet review.

Statistical analysis

Kappa and weighed-kappa scores were calculated using Cohen's κ for pairs of observers. All other statistical analysis was performed using an SPSS database. Positive and negative predictive values were calculated for gross SF analysis.

RESULTS

Development of the standardised questionnaire

Twenty-two SF samples were collected for the pilot study. In 10 (45%) of the samples, two observers differed slightly in their responses to the questionnaire. Despite these minor discrepancies, the conclusion reached by the pair of observers examining the synovial fluids differed in only 2 (9%) samples. The description of colour differed in 5 samples, clarity in 4 samples and viscosity in 2 samples. For colour the difference was mainly in differentiating between yellow and yellow green (3 samples).

The conclusions of four observers who interpreted the results of 22 questionnaires without themselves directly assessing the synovial fluid showed good agreement with a mean κ score of 0.889. The four observers only disagreed on the diagnosis of 2 (9%) synovial fluids.

The results from the initial testing of the "standardised questionnaire" suggest that it can be completed with only minimal discrepancies occurring between observers. Furthermore, the final diagnosis following detached interpretation of the questionnaire shows good agreement across different observers. It was concluded that in the hands of physicians with rheumatological training, the questionnaire can be completed and interpreted reliably.

Patient demographics

Table 1 shows patient demographics. A total of 63 (78%) patients had a known rheumatological diagnosis: osteoarthritis, 20 (25%); rheumatoid arthritis, 21 (26%); crystal arthritis, 12 (15%); seronegative arthritis, 6 (7.5%); connective tissue disease, 3 (4%); reactive arthritis, 1 (1%). Eighteen patients were on DMARDs: hydroxychloroquine (n = 2), methotrexate (n = 8), sulphasalazine (n = 5), gold (n = 1), leflunomide (n = 1) and azathioprine (n = 1). None of the patients in this study were on anti-tumour necrosis factor drugs.

The most common site of aspiration was the knee joint in 73 (91.3%) patients. Other joints involved were knee bursa in 2 (2.5%), shoulder in 2 (2.5%) and ankle in 2 (2.5%) patients. Aspiration site was not recorded in 1 (1.3%) patient.

Gross analysis

Gross analysis was performed on all 80 SF samples using the questionnaire. Fluid was categorised as non-inflammatory in 28 (35%), inflammatory in 48 (60%) and potentially septic in 4 (5%) by the physicians.

Cell counts

Cell counts were performed on 72 samples. The remaining 8 samples were too small for cellular analysis. A total of 37 (45%) were in the non-inflammatory range, 33 (31%) were inflammatory and 2 (2.5%) potentially septic. When the cell count results were compared to gross analysis, fewer samples were found to be inflammatory (fig 2).

Final diagnosis and synovial fluid cell count analysis

Table 2 illustrates SF cell count and range for final diagnosis.

Crystal analysis

A total of 79 (98.8%) samples were sent for PLM, of which 26 (35%) were positive for crystals.

Calcium pyrophosphate crystals were detected in 16 (21%), uric acid crystals were present in 8 (10%) and hydroxyapatite crystals (using Alizarin red stain) in 2 (2.5%).

Gross analysis was inflammatory in 19/26 samples. In the remaining 7, it was non-inflammatory in 5 (cell count also non-inflammatory in 2, inflammatory in 1 and not known in 2) and septic in 2 samples.

Bacteriological analysis

Synovial fluid culture was performed on 79 (98.8%) samples, of which 4 (5%) were positive. Two samples were positive on both Gram stain and culture and two were culture positive only. For the patients with proven septic arthritis, gross analysis was more sensitive than cell count (fig 2).

Synovial fluid from two patients who subsequently turned out to have crystal arthritis were initially categorised as potentially septic on gross analysis.

Inflammatory arthritis

Thirty-one patients in this study were known to have an inflammatory joint disease (excluding crystal arthritis). On case notes review, four of these patients were thought to have the effusion secondary to osteoarthritis rather than flare up of the original inflammatory arthritis. Both gross and cell count analysis indicated non-inflammatory fluid in all four samples. However, cell count analysis was non-inflammatory in a further 12 samples; five of these patients were on DMARDs (methotrexate, n = 3; sulphasalazine, n = 2).

Non-inflammatory arthritis

Twenty patients had a final diagnosis of osteoarthritis. For this group of patients there was 100% agreement between gross analysis and cell count findings (fig 2).

Table 1 Patient demographics

No of patients	80
Age (y), mean (range)	65 (23–97)
No seen in outpatient department (%)	53 (66)
Patients with a known rheumatological diagnosis, no (%)	63 (78)
Patients with known inflammatory arthritis, no (%)	43 (54)
Patients on DMARDs, no (%)	18 (24)
Monoarthritis, no (%)	54 (68)

DMARDs, disease modifying antirheumatic drugs.

Cell counts and gross analysis in comparison

Sensitivity of gross analysis in determining whether a fluid was inflammatory or non-inflammatory was 94% with a specificity of 58%. The positive predictive value was 0.69 and the negative predictive value was 0.91.

DISCUSSION

BSR and ACR guidelines recommend that when assessing patients with a joint effusion gross analysis, PLM, cell counts and microbiological assays are performed. Other tests such as mucin clot test, glucose, protein and pH studies have been shown to be less effective.¹¹

The standardised method of documenting gross analysis of synovial fluid was found to be helpful, especially when the synovial fluid specimen was unavailable to view. Where the fluid was noted to be non-inflammatory on gross analysis, this was confirmed on cell count; under such circumstances we would recommend that a cell count is not required. When gross analysis suggests an inflammatory effusion, correlation with cell count is poor. There may be several reasons for this.

Firstly, various cell count ranges have been described in the literature for defining the three major groups (non-inflammatory, inflammatory and septic). The cell count range used by Freemont *et al*¹² is different to the one used in this study, which could account for the discrepancy between cell count and gross analysis diagnoses for inflammatory joint disease and septic arthritis. We have not looked at the differential SF cell count, which again has been suggested as helpful.

In our laboratory the reference method for analysing SF cell count was the use of a cytometer and microscope. The reliability of this test has been little studied. The available quality control studies indicate that there is great variation among and within laboratories in manual counting of white blood cells in SF.^{13–14} A recent study¹⁵ has shown automated cell counting using the DIFF channel of Sysmex XE-2100 to produce more precise and faster results. Repeating this study using automated cell count methodology might produce different results.

Final diagnosis for each patient was extracted from the case sheets retrospectively rather than individually reviewing each patient, which could pose a problem in interpreting the results, as in usual practice the final diagnosis sometimes changes at follow-up visits.

Due to the design of the study the physician analysing the gross analysis of synovial fluid was usually aware of any known rheumatological diagnosis which could have led to physician bias in interpreting the gross analysis results, especially in patients with inflammatory joint disease. In addition, 23% of patients were on a DMARD, which may have affected the final SF cell count although none of them had low peripheral blood white cell counts.

Septic arthritis is a rheumatological emergency and delay in diagnosis and treatment can lead to irreversible joint damage, significant morbidity and even mortality.¹⁶ The two patients with proven septic arthritis in this study were both picked up on gross analysis, and management was initiated even before Gram stain results were made available. For one patient the cell

Figure 2 Agreement between gross analysis and cell counts for each final diagnosis.

count was found to be inflammatory rather than septic, therefore cell counts alone are unreliable. In a case series of patients with coexisting gout and septic arthritis, three patients had cell counts <6000.¹⁷ Cell count results for septic arthritis were similar.¹⁷

Joint effusions present as a diagnostic challenge to physicians and need careful evaluation and interpretation of both clinical and laboratory findings to make accurate diagnosis, initiate appropriate management and avoid unnecessary hospital stay.

The standardised method of documenting gross analysis of synovial fluid was found to be helpful by both junior and senior medical staff. We recommend that it is used in daily practice. This information could be incorporated on to laboratory request forms and be reported by the laboratory staff at the time of analysis. This would ensure that this test is performed reliably and is consistently available to clinicians making treatment decisions. Where the fluid is non-inflammatory on gross analysis, a synovial fluid white cell count cannot be recommended. The place of a white cell count in the management of patients with potential inflammatory arthritis cannot be determined from this study. However, a white cell count in the inflammatory range cannot reliably be used to exclude septic arthritis. Until further work is done to standardise laboratory cell count methodology, the use of a standardised gross synovial fluid analysis should be performed in preference to a laboratory white cell count.

Table 2 Range of synovial fluid (SF) cell counts and median for each diagnostic group

Diagnosis	n	Cell count range (cells/mm ³)	Median (cells/mm ³)
Osteoarthritis	18	5–960	70
Rheumatoid arthritis flare	17	86–10000	1800
Seronegative arthritis	6	16–7500	1820
Reactive arthritis	4	4500–36800	14850
Crystal arthritis	22	95–70000	3675
Septic arthritis	2	23000–70000	46500
Bursitis	1	4000	
Traumatic effusion	2	25–8200	4112

The median SF cell counts for rheumatoid arthritis flare and seronegative arthritis are in the non-inflammatory cell count range.

Take-home messages

- Gross analysis is a useful test to differentiate between inflammatory and non-inflammatory synovial fluid.
- If the synovial fluid is non-inflammatory on gross analysis, performing a cell count may not add to the diagnosis.

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