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Leaders

Microscopic analysis of synovial fluid—the perfect diagnostic test?

Generally the gold standard in all fields of disease diagnosis is the "tissue" analysis performed by the histopathologist. Why, therefore, is histopathology one of the least used investigations when it comes to the diagnosis and management of rheumatological disorders? Could it be that the demands of rheumatological medicine are beyond the grasp of the average histopathologist? This might be true but is it not a mistake to suggest that the complexities of renal medicine, gastroenterology, hepatology, dermatology, neurology, etc are less testing than those of rheumatology? Yet in these specialties the histopathologist plays a central diagnostic role. In fact the reality lies not in the intellectual problem but in the nature of the tissue.

There are only four components to each synovial joint: capsule, articular cartilage, synovium, and synovial fluid. It is generally held that the responses of these tissues to disease are limited and insufficiently specific to be used as the basis of a diagnostic test. With a few notable exceptions, biopsy of the capsule, cartilage, and even the synovium is indeed of limited diagnostic value in rheumatological practice, but is the same true of the synovial fluid?

The objective evidence has always indicated a diagnostic role for synovial fluid analysis[1–4] and for 12 years we, in osteoarticular pathology in Manchester University, have sought to generate evidence that synovial fluid microscopy has a particular place in the diagnosis of joint disease.[5–10] As evidence of our success in this context we quote the widespread use of our diagnostic service by our front line clinical colleagues. It is our claim that if the patient has sufficient synovial fluid to aspirate (0.5 ml or more), synovial fluid microscopic analysis should be the first, and in many cases need be the only, diagnostic investigation. Furthermore it is the only test in existence which can be applied to diagnosing the full spectrum of joint disorders from rheumatoid disease to a torn meniscus, from multicentric reticulohistiocytosis to septic arthritis, and from a seronegative spondylarthropathy to gout, and as such represents a valuable diagnostic screening test. Our experience also indicates that synovial fluid microscopy gives prognostic data[11] and is a useful research tool.[12–14] It is cheap, effective, simple, and reliable; but outside our region it is also one of the least used tests in rheumatology—why?

The most probable reason is that too few laboratories offer the investigation and too few clinicians demand it. Our experience is that, if the test is offered and properly delivered by laboratories understanding the needs of rheumatologists, experienced specialist clinicians and financially aware trusts are only too willing to use the service.

The test

Normal synovial fluid is a transudate of plasma supplemented with high molecular weight sacchariderich molecules, notably hyaluronans, produced by type B synoviocytes. Synovial fluid differs from all other body fluids in that the surface of synovium and cartilage are not covered by a cell layer with an intact basement membrane, but an incomplete layer of cells. Thus the matrix of cartilage and synovium are in contact with the synovial fluid, allowing a relatively homogeneous chemical environment within the joint.

Because of this peculiar relation between the tissues in the joint, variations in the volume and composition of synovial fluid reflect pathology, and chemically mediated events occurring within the synovium and cartilage—such as inflammation and enzyme mediated degradation—are reflected in changes in the synovial fluid. These include changes that lead to the presence of non-cellular particulate material within the joint and the production of factors leading to accumulation of different cell types within the synovial fluid. This is the basis of the understanding of synovial fluid microscopy. Thus synovial fluid microscopy has two aspects: examination for particulate material and cytoanalysis.

Cytoanalysis of synovial fluid differs in two important regards from that of other body fluids or exfoliated cells. First, synovial joints are very rarely affected by neoplastic processes. Second, the greatest diagnostic information comes not only from the recognition of cell types but also from their quantification[15].

Synovial fluid examination in our laboratory follows a four part sequential analysis: (1) gross analysis; (2) an assessment of the number of nucleated cells; (3) microscopic analysis of unprocessed synovial fluid—the "wet prep"; (4) microscopy of a stained cytocentrifuge preparation. All the parts can be carried out in any routine cytology laboratory and each contributes to making a diagnosis.

Gross analysis

Because synovial fluid from inflamed joints can clot it should be anticoagulated. However it cannot be fixed and

even with refrigeration the optimum cytological information can only be extracted from the sample if it arrives in the laboratory within 48 hours of aspiration, and preferably as soon as possible within the first 24 hours. This is a major limitation of the test. When the specimen arrives in the laboratory it is first examined macroscopically to assess colour, clarity, viscosity, and the "mucin clot", crude benchtop investigations which give information on the presence of blood, particulate material, and neutrophil and macrophage derived enzymes.

The nucleated cell count

The number of nucleated cells within the synovial fluid specimen is one of the most important diagnostic and prognostic criteria and allows "inflammatory" and "non-inflammatory" fluids to be distinguished and the "extent" or "degree" of any inflammatory process present to be assessed.[7 8 15]

"The wet prep"

This preparation is examined for one type of cell, the ragocyte,[16] and several different classes of noncellular particulate material. The ragocyte is any phagocyte containing large intracytoplasmic granules. Typically in rheumatoid disease they contain immune complexes, but they are also seen in septic and other inflammatory arthropathies. Their number is key to making the diagnoses of rheumatoid and septic arthritis. The non-cellular material includes organic and inorganic crystals[17–23] and fragments of joints such as cartilage, meniscus, and ligament.[6] This part of the test contributes significantly to the differential diagnosis of inflammatory arthropathies and intra-articular trauma and wear in prosthetic joints[24].

Many modern plastics such as HDPE and methyl methacrylate, and composites such as Dacron and carbon fibre, mimic crystals should they fragment, thus causing diagnostic problems. Metal debris from metal based prostheses can be shed or abraded and appear as tiny black particles. These may be difficult to recognise but are important as they are harbingers of imminent prosthetic failure.[15]

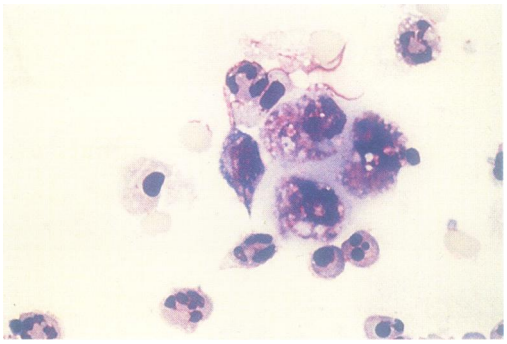
Occasionally peculiar extraneous material is found within the joint, usually introduced by a clinician or at the time of articular trauma.[15]

The cytocentrifuge preparation

This is a specially prepared, stained cytological preparation and completes the diagnostic armamentarium, allowing diagnoses to be made within the broad subgroups of inflammatory and noninflammatory arthropathies by distinguishing the types and relative proportions of morphologically identifiable inflammatory cells (figure).[5–15] It is also used for identifying or excluding different organisms in cases of suspected non-viral infective arthritis, most commonly caused by gram-positive cocci but increasingly other bacteria and fungi.[15]

The clinical value of synovial fluid microscopy

By retrospective analysis of proven cases it is possible to recognise microscopic patterns specific for certain of the arthropathies. These we have summated into a diagnostic algorithm.[8–15] In one prospective analysis of 1000 synovial fluids, completely blind analysis gave an exact diagnosis in approximately 50% of cases and in a further 46% produced diagnostic and prognostic data of value in clinical practice. When typically rudimentary clinical data were added, the exact diagnostic rate increased to 64% but there was no reduction in the 4% of undiagnosable cases.



A synovial fluid cytocentrifuge preparation showing lymphocytes, viable and apoptotic polymorphs, and a cytophagocytic macrophage.

Synovial fluid microscopy is of greatest value in distinguishing inflammatory from non-inflammatory arthropathies, in defining specific disorders within these two groups, and in the diagnosis of a patient with a mono- or oligoarthropathy. In this context synovial fluid microscopy is particularly important in the diagnosis of early inflammatory joint disease where it is often possible, on the basis of cytology, to identify a specific syndrome or at least distinguish between rheumatoid disease, seronegative spondylarthropathies, and other inflammatory arthropathies before the full clinical picture develops. Finally it allows the very rapid diagnosis of joint disease, particularly in disorders such as septic arthritis where the prognosis is inversely related to the delay in diagnosis.

Synovial fluid analysis requires a full independent evaluation as a diagnostic tool and standardised analytical procedures.[26] We are absolutely convinced, however, that with collaboration between clinicians and pathologists, synovial fluid microscopy can be established in any hospital cytology department and within a year that hospital will have a novel and powerful diagnostic and research tool.

A J FREEMONT

Department of Osteoarticular Pathology,
Stopford Building, The University of Manchester,
Oxford Road, Manchester M13 9PT,
United Kingdom

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Surfing for rheumatologists—a guide to rheumatology resources on the Worldwide Web

Terms such as Internet and Worldwide Web (WWW) may have passed into common usage, but to many people the idea of "surfing the net" is about as likely as walking on the moon. However, for devotees, communicating by electronic mail, participating in newsgroups, and managing Web pages has become an integral part of daily life.

The rheumatological community appears to reflect this polarisation. On the one hand there are those who have embraced the new technology and are already exploring avenues for its use in clinical practise, research, and the general dissemination of information. On the other hand there are those for whom a computer is at best a word processor and at worst a phobia.

Many in the field of rheumatology are asking whether it is worth investing time, effort, and money in this new technology. Is the WWW a seven day wonder or will it have a major influence on the practise of rheumatology in the future? Quite clearly the impact that computer technology has already made on medicine and medical research is immense. The development of the information superhighway is a logical progression in this rapid evolution which amplifies the effectiveness of the stand-alone computer by providing a link to millions of other computers. Each computer links to a host, which in turn is connected to a regional centre, which in turn is linked to national and international gateways, hence the concept of a "web"-like structure of communication. In theory, this quantum leap in technology should result in profound changes in the way rheumatologists and allied professionals interact with each other, with patients, with other interest groups and with the world in general.

The potential of the Web is vast. It is already possible to send text, graphics, data, software, photographs, sound, movies, and even money to another Web user anywhere in the world within seconds. One recent highly publicised example was the potential use of the Internet to allow battlefield surgery to be performed by robotic arm while the surgeon "operated" from the safety of a hospital hundreds of miles behind the front line.[1] Perhaps a physician wants to obtain a second opinion on an *x* ray or MRI scan from a colleague in another hemisphere. This is possible over the internet in minutes. Likewise, an operator can attach a patient to an ECG machine in one city and a physician can view and analyse the traces in another. There is, however, one urgent problem which needs to be addressed for all internet communications and that is the relative lack of security on the Web, which is particularly important where patient confidentiality is concerned.

Other features of the internet are also making an impact on the medical environment. Videoconferencing through high speed Web links could be a cheap alternative to organising costly international meetings. Whole virtual communities and discussion groups have already developed on the Web. Individuals from all parts of the world who are never likely to meet in person are able to share information and interests on a daily basis. Distance learning takes on a whole new meaning when comprehensive multimedia course material is available on-line to students in any continent at any time of night or day. Essays can be submitted, marked, and discussed electronically without tutor ever having to meet student.

Aside from the obvious sociological implications of the new technology, other pitfalls in the information superhighway are becoming apparent. The question of the moment is whether current investment in the infrastructure and management of the network will cope with the phenomenal growth in usage which is predicted for the next few years. Already there are an estimated 12 million computers connected worldwide, supporting over 70 million unique pages of information on the Web. At peak times, when the majority of US citizens are awake, accessing popular overseas Web sites can be a severe test of patience. The slowdown in data transfer can be such that it becomes impractical to download anything more than one or two pages of text. Furthermore, when searching for rheumatology information, Web pages are not peer reviewed or edited for content. For example, it is possible to find a comprehensive guide to the management of fibromyalgia written by a world authority on one page and a recipe for the latest herbal suppository to cure all forms of arthritis on another. It is therefore important not to treat the Web as an encyclopaedia. The quality and authenticity of information provided must always be viewed in the context of its source.

Medical and scientific publishing is also being affected by this revolution. Most publishing companies are developing electronic versions of books and journals, either on CD-ROM or in a form that can be downloaded from the Internet on payment of a subscription. In many cases, medical and scientific journals now accept manuscripts