Diagnosis of “Rheumatoid Variants”

Ankylosing Spondylitis, the Arthritides of Gastrointestinal Diseases and Psoriasis, and Reiter’s Syndrome

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Four rheumatic diseases—ankylosing spondylitis, the arthritis accompanying ulcerative colitis or regional enteritis, psoriatic arthropathy, and Reiter’s syndrome—formerly considered to be forms of rheumatoid arthritis, are now distinguished from that disorder and should be recognized by the physician as entities. These arthritides may be distinguished from each other by a number of clinical and radiographic characteristics, principally (1) the roentgenographic appearance of the spine when spondylitis is present, (2) the location of periosteal new bone formation, (3) the location of arthritis in the joints of the limbs, and (4) the presence of characteristic skin lesions.

THE RHEUMATIC DISORDERS which can produce widespread spondylitis were formerly regarded as “variants” of rheumatoid arthritis. Because of significant clinical and pathogenetic differences between them and rheumatoid disease, they now are accorded status as separate entities. However, the term rheumatoid variants retains some utility to denote a group of diseases with some striking similarities: ankylosing (formerly rheumatoid) spondylitis, the arthritis which sometimes accompanies ulcerative colitis or regional enteritis, arthritis with psoriasis, and Reiter’s syndrome. Because these disorders are characterized by their ability to affect both the spine and the peripheral joints, they also have been called “spondylo-

arthropathies.” In this paper we review similarities and differences of members of this group as they apply to diagnosis and differential diagnosis.

Spondylitis

Rheumatoid arthritis of adults, when it affects the spine, usually is confined to the cervical area; the lumbo-sacral spine is not often involved. The spondylo-arthropathies are distinguished by their production in some victims of inflammatory disease of the spine which can involve the entire length of the vertebral column. The character of the spondylitis serves to divide these diseases into two subgroups, as described in a study in which one of us (T.R.) participated. McEwen and his associates first called attention to differences between ankylosing spondylitis and spondylitis with ulcerative colitis on one hand, and the spinal disease accompanying psoriasis and Reiter’s syndrome, on the other. Spinal inflammation of anky-
RHEUMATOID VARIANTS

Figure 1.—Roentgenogram of a segment of lumbar spine of a patient with ankylosing spondylitis, showing ossification of spinal ligaments at borders of anulus fibrosi. The syndesmophytes arise from the margins of the vertebral bodies.

Figure 2.—Roentgenogram of a segment of lumbar spine of a patient with psoriatic spondylitis, showing ossification of spinal ligaments distant from the anulus fibrosi. Syndesmophytes arise from the mid-portions of the vertebral bodies (non-marginal), and may be hook-shaped or comma-shaped.

Ankylosing spondylitis and gastrointestinal disease (either ulcerative colitis or Crohn’s disease) is expressed by calcification of ligaments (syndesmophytosis) immediately adjacent to the intervertebral discs (Figure 1). But in 50 percent or more of cases of spondylitis associated with psoriasis and Reiter’s disease, syndesmophytes form also in the outer layer of para-spinal ligaments (Figure 2), an observation first reported by Bunim. Ankylosing spondylitis and that accompanying enteric disease can therefore be grouped in a category 1, while the spinal arthritides of psoriasis and Reiter’s syndrome constitute a category 2. A close relationship between psoriasis and Reiter’s syndrome has also been proposed on grounds of clinical and other radiologic similarities.

Ankylosing spondylitis is a prototype of subgroup 1. Several reviews of this disease have recently been published. It is predominantly a disorder of young men, usually beginning with back pain and stiffness. Systemic symptoms—fever and weight loss—may be present. Bilateral sacro-iliitis occurs in almost every case; inflammation usually follows an ascending pattern and may eventually extend to the cervical spine. Involvement of costochondral and manubrio-sternal joints often is present but overlooked. This disorder can and should be diagnosed long before the characteristic flexion deformity of the spine develops; such deformity in most instances can be prevented if the importance of proper posture is conveyed to the patient early and repeatedly.

In about 5 percent of patients with ulcerative colitis extensive spondylitis develops; unlike the peripheral arthritis which accompanies this disease and is described below, the spondylitis tends to progress independent of the activity of the enteric disorder and even after colectomy. Sacro-iliitis alone is more common than disease involving additional areas of the spine, and can be demonstrated in nearly 20 percent of patients.
The incidence of spinal arthritis rises with increasing duration of disease, but spondylitis can precede the enteric symptoms.

Reliable estimates of the prevalence of all degrees of spondylitis in patients with psoriasis are not available, but large numbers of cases have been reported and the condition cannot be rare. Sacro-iliitis has been found in about 20 percent of psoriatic subjects.16

Figures given for the frequency of spondylitis in Reiter's disease have varied greatly (up to 50 percent). In the large group of postdysenteric cases in Finland, after a 20-year interval spondylitis had developed in at least 10 percent.16 It is more frequent among patients with chronic or recurrent disease. Once again, involvement of the sacroiliac joints alone often is encountered without evident disease in more cephalad parts of the spine.16,17

Sacro-iliitis is thus a finding common to the whole group, but it differs between the two sub-groups in that it tends to be more severe with diseases of category 1, and may be asymmetrical with those of category 2.

Patients with spondylitis accompanying colitis, psoriasis or Reiter's syndrome should not be listed on hospital records and other documents as having "ankylosing spondylitis," since that diagnosis is properly applied only to the idiopathic, primary spinal arthritis usually seen among young men. In order to make clear the relationship of secondary spinal disease to the primary process, such patients should be labeled as having "colitic spondylitis," "psoriatic spondylitis," "spondylitis with Reiter's syndrome," or similar terms.

Periostitis and Related Manifestations

Another set of findings which helps to differentiate the spondylo-arthropathies are those produced by periosteal (and sometimes fascial) new bone formation. Particularly in ankylosing spondylitis, periosteal inflammation about the pelvis may produce pain. Roentgenograms made after the disease has been present for several years may show toothbrush-like "feathering" of the margins of the ischial rami and tuberosities or iliac crests. Pelvic periostitis occurs less frequently in the other forms of spondylitis.9

Calcaneal spurs, produced by periostitis or by plantar fasciitis or by both, are encountered most frequently in Reiter's disease, especially chronic cases (Figure 3).18 Because of the venereal associations of that disorder the resultant abnormality has been called "lover's heels." However, spurs are not uncommon in association with ankylosing spondylitis and have been reported with psoriatic spondylitis as well. We have also noted, in many cases of Reiter's syndrome or ankylosing spondylitis, pain or tenderness circumferentially about the heel rather than on the plantar surface. This we suspect also is caused by periostitis, although roentgenograms do not ordinarily show such abnormality. Symptomatic localized periostitis has been described at a number of sites in patients with Reiter's disease.19

More specific is the occurrence of fluffy, diffuse periosteal new bone formation along long bones, which sometimes is seen in chronic cases of the diseases of category 2.18 With psoriatic arthritis, bones of the hands and fingers often are affected, while in Reiter's disease bones of the feet and
toes are more commonly involved. The sites of the manifestation thus parallel the more common location of peripheral joint disease in these two disorders.

**Peripheral Arthritis**

Another feature separating the two subgroups is the nature of the peripheral arthritis. Ankylosing spondylitis is the only one of these disorders which primarily affects the spine, but even in this disease non-axial joint involvement is common.\textsuperscript{10,20} It can take three forms:

1. Arthritis involving one or a few large joints (such as hip, knee, or ankle), which precedes or begins simultaneously with the spinal symptoms in about one-third of cases.\textsuperscript{7,8} This usually is self-limited. We have been sufficiently impressed by the frequency of antecedent peripheral large joint disease in ankylosing spondylitis that when a young man presents with an otherwise undiagnosed pauciarticular, we suspect that spondylitis may become manifest later.

2. Following spondylitis of some duration, arthritis may appear at limb girdle joints (shoulders, hips) and knees.

3. In a small number of patients with ankylosing spondylitis, a peripheral polyarthritis resembling rheumatoid arthritis develops.

Peripheral arthritis appears in at least 15 percent of patients with ulcerative colitis, especially those with severe disease or other extra-intestinal manifestations.\textsuperscript{11,12} It is episodic, most attacks not lasting more than two months. Usually only a few joints are involved. In its acute onset and migratory spread, the arthritis may resemble that of rheumatic fever. It differs from rheumatoid arthritis in its predilection for large joints (knees, ankles, elbows), in its asymmetrical involvement of joints, and in the fact that it does not produce deformity. As is true of all the “rheumatoid variants,” the peripheral arthritis may precede the primary (in this case, enteric) manifestations of the disease. Peripheral joint symptoms commonly vary in parallel with the severity of the bowel symptoms, and may disappear after colectomy. However, the treatment of colitic arthritis is primarily that of the basic disease, and the joint disorder should never be a reason for colectomy.

A smaller proportion of patients with regional enteritis (Crohn's disease) likewise develop mild arthritis, which may involve small joints of the hands as well as the knees, ankles and other large articulations.\textsuperscript{21,22}

Involvement of the joints of the limbs in subgroup 2 tends to differ from that just described in that it is more peripheral. Approximately 7 percent of patients with psoriasis are said to develop arthritis.\textsuperscript{15} Articulations of the upper limbs are more commonly affected,\textsuperscript{23} and the distal interphalangeal joints of the fingers are involved in as many as two-thirds of cases.\textsuperscript{1} Since these joints are seldom affected by ankylosing spondylitis, enteric arthropathies, or rheumatoid synovitis, finding inflammation at this site is valuable for differential diagnosis. Marked destruction of the joints of the hands (arthritis mutilans) results from psoriatic arthritis more frequently than from other common arthropathies. Resorption (“whittling”) of the terminal phalanges sometimes is seen.

Reiter's disease more often involves the lower limbs: knee, ankle, tarsal and toe joints.\textsuperscript{17,24} The “sausage toe” (Figure 4), uniformly swollen along its length because of inflammation at both interphalangeal joints, is characteristic of this syndrome (but also can be seen accompanying psoriasis). Distal interphalangeal joints of fingers may also be affected in this disorder.\textsuperscript{8} Episodes of arthritis in Reiter's disease commonly involve a few joints in an asymmetrical manner, and last several months.\textsuperscript{25} Articular inflammation may be chronic or recurrent,\textsuperscript{26,27} and may be the only presenting symptom, the ocular or genital manifestations having been fleeting or unnoticed. Permanent damage to the joints can occur when the arthritis is chronic.\textsuperscript{16,28}
Skin Lesions

A fourth point of difference between the two subgroups of the spondylo-arthropathies is the presence of specific eruptions in subgroup 2. Psoriasis is required for a diagnosis of psoriatic arthropathy, but the skin lesions may be much less evident than the rheumatic disease, or they may appear only after joint disease has developed. On any patient in whom spondylitis or arthritis consistent with psoriatic arthropathy appears, particularly if the distal interphalangeal joints of the fingers are affected, small psoriatic lesions should be carefully sought at the fingernails (frequently pitted on digits where the distal joint is inflamed), scalp, umbilicus and gluteal crease. Atypical forms of psoriasis are said to be more common among those patients who have associated joint disease.\(^{28}\) The atypical lesions include pustular psoriasis of the palms and soles, which is indistinguishable from the eruption of Reiter's syndrome, even under the microscope.

Distinctive skin lesions are seen on over a quarter of patients with Reiter's disease, changing the classical triad of symptoms—arthritis, urethritis and conjunctivitis—to a tetrad. (These elements need not occur simultaneously, but can be widely separated in time, with a recurring or chronic disease.) Inflammatory, hyperkeratotic skin lesions, called keratoderma blennorrhagicum because they formerly were ascribed to gonorrhea (blennorrhagia), occur most often on the glans penis, but may appear on the palms, soles, or elsewhere. On the uncircumcised penis the hyperkeratotic appearance is lost, and shallow erosions are seen; histologically, this balanitis is identical with the skin lesions elsewhere.\(^{26,29}\) Balanitis, when it occurs, is a very useful distinguishing feature. Ulcerations of the oral mucosa also occur, but may not be noticed unless specifically sought.

In contrast, specific eruptions are not seen in association with the diseases of category 1. Erythema nodosum and pyoderma gangrenosum sometimes occur with ulcerative colitis.

Other Manifestations

Inflammation of the eyes and aortic root can develop as a manifestation of any of the diseases under discussion. Their presence in a patient with arthritis should lead to consideration of this group of disorders, but is not of much help in distinguishing among the spondylo-arthropathies. Uveitis or iritis occurs in approximately 10 to 20 percent of patients with ankylosing spondylitis, and may be the presenting symptom.\(^ {7,8}\) Among all patients with ulcerative colitis, uveitis occurs in about 5 to 10 percent, but it is much more common in those with associated spondylitis or peripheral arthritis.\(^ {12,14}\) Such patients also frequently exhibit conjunctivitis.\(^ {12}\) Inflammation of the uveal tract is found less often with regional enteritis.\(^ {50}\) Iridocyclitis is quite common in those cases of Reiter's syndrome in which there are multiple recurrences;\(^ {19}\) it is reported to be more frequent in patients with sacro-iliitis.\(^ {31}\) With this disease keratitis, episcleritis and of course conjunctivitis also are seen.\(^ {17}\) Uveitis occurs only rarely with psoriatic arthritis.\(^ {32}\)

Inflammation and fibrosis at the root of the aorta develop in a significant number of cases of ankylosing spondylitis, producing aortic regurgitation and/or cardiac conduction defects (particularly heart block); the frequency of either of these manifestations is as great as 8 percent.\(^ {8,33}\) At least one case of aortitis in association with colitis and spondylitis has been noted.\(^ {34}\) Aortitis resembling that of ankylosing spondylitis is being reported with increased frequency as a manifestation of chronic Reiter's syndrome;\(^ {38}\) cardiac conduction defects can occur with or without valvular disease. Similarly, aortic regurgitation and heart block have been found in association with psoriatic spondylitis.\(^ {28}\)

While the presence of gastrointestinal symptoms is expected when arthritis is associated with colitis or enteritis, it should be pointed out that Reiter's syndrome can occur following acute enteritis, either epidemic\(^ {56}\) or sporadic.\(^ {30}\) In the latter case it is possible that diarrhea is a manifestation of the Reiter's disease itself.\(^ {25}\)

Laboratory Diagnosis

Other than the roentgenographic features already mentioned which are of diagnostic value (for example, pelvic periostitis in ankylosing spondylitis, whistling of the phalanges with psoriatic arthropathy, calcaneal spur with Reiter's syndrome), laboratory investigations contribute little to the identification of these diseases. The rheumatoid factor (antiglobulin antibody) usually present with rheumatoid arthritis is not commonly found associated with "rheumatoid variants." Other tests may show non-specific abnormalities common to any inflammatory disorder, such as an elevated erythrocyte sedimentation rate.
Patients with spondylitis may be found to have unsuspected cardiac conduction defects if electrocardiograms are obtained.

**Differentiation from Rheumatoid Arthritis**

As their former classification as “variants” of rheumatoid arthritis suggests, these diseases are most often mistaken for rheumatoid arthritis if an error in diagnosis is made. Any of the following features manifested by an adult patient who at first appears to have rheumatoid disease should lead to consideration of the disorders discussed in this paper:

- Arthritis involving a few large joints, and sparing the small joints of the hands, wrists and feet.
- Arthritis involving distal interphalangeal joints of the fingers or interphalangeal joints of the toes.
- Low back pain or stiffness.
- Pain in or tenderness of the heels.
- Uveitis.
- Skin lesions.
- Any recent or chronic abnormality of bowel habits or stools.
- Periostitis on x-ray examination.

It should also be noted that, whereas most patients seeking medical attention for rheumatoid disease are women, ankylosing spondylitis and Reiter’s disease (except when it follows epidemic dysentery) are almost exclusively afflictions of men. Characteristic patterns of clinical manifestations of the spondylo-arthropathies, which aid in their identification, are shown in Table 1. This is presented as a guide giving emphasis to features of diagnostic value, and is not intended as a comprehensive clinical description.

**REFERENCES**

RHEUMATOID VARIANTS


Practical Tips on Inducing Ovulation (Oligo-Ovulation)

“When do you give human chorionic gonadotropin (hCG); and do you use one dose or two?”

We give one injection of 10,000 international units of hCG four days after the last dose of Clomid® in the original sequence; and the hCG is given 48 hours after the last dose of Pergonal® in the second prolonged sequence. In other words, if a dose of Pergonal, or a sequence of Pergonal, has resulted in a 4 plus fern test, we then wait 24 hours and on the following day give the hCG in one dose. The patient is then advised to have intercourse the day after the hCG injection, because ovulation usually occurs within 24 to 30 hours of the hCG.

In an effort to diminish luteal phase insufficiency, we give an additional dose of hCG, 2,000 international units, four days after the first injection of hCG.

Another question that has been asked is, “Should progesterational agents or progesterone be used after ovulation induction in this sequence?” Ordinarily we do not, but in patients who have given evidence of being aborters, or habitual aborters, we do begin a progesterational agent if the basal body temperature remains elevated 18 consecutive days, from the low point, even before the pregnancy test is positive. This would then be approximately 10 to 14 days after the second hCG injection. We would then use a preparation such as Delutev®.

Another question is, “Should hydrocortisone be used in any of these sequences?” And I would say, in general, no, but if there are certain patients (and there are a few) in whom the 17 ketosteroids are elevated in the range of 15 to 20, and in whom the diminution in 17 ketosteroids is seen after the administration of hydrocortisone, we do treat these patients with hydrocortisone and with Clomid; and there are certain patients in whom I believe a double-organ defect is present and I think ovulation will only result with this double attack.

Another question, “Should estrogen be given with Clomid?” For years, I advocated the use of estrogen-priming prior to the use of Clomid, but then subsequently gave that up. I now would say that if a patient has had prolonged amenorrhea, say for five or six months, I would prime that patient with estrogen, for example ethinyl estradiol, 0.05 mg twice daily for 20 days, and permit her to have a withdrawal flow, and then try that again. Now, I know that this dose is an ovulation suppressive one and some physicians may object to this and may like to give lower doses. In any event, I think that some priming of the endometrium should be done prior to the sequence in which pregnancy is desired—since, if the endometrium is abnormal or insufficient, abortion may occur. We are also now using a low dose of estrogen (ethinyl estradiol) 0.02 mg from day five through day twelve of the cycle in order to prevent the anti-estrogenic effect of the Clomid on cervical mucus. “How long should one treat patients with these agents (Clomid, Clomid-hCG, Clomid-Pergonal-hCG)? How long should one utilize these sequences before giving up?” I don't know the answer to that question, but I would say usually six to nine cycles should be tried. After all, in a normal couple, where everything is normal, having intercourse four to five times weekly, the woman will only become pregnant in 53 percent of cases within six months. Therefore, I do not believe that the three-cycled treatment of Clomid is adequate, particularly if you suggest that the patient not become pregnant during the first cycle . . . or second cycle if she has had prolonged amenorrhea before. Therefore, we treat our patients for at least six consecutive cycles. I've had one patient become pregnant during the eighth cycle of the Clomid-hCG sequence. I've had another become pregnant on cycle ten, and I think others have had pregnancies occurring as late as cycle twelve.

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