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FITZPATRICK'S
DERMATOLOGY
IN GENERAL
MEDICINE

SIXTH EDITION

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FITZPATRICK'S DERMATOLOGY IN GENERAL MEDICINE

Sixth Edition

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22. Schmidt-Egenolf M et al: Oligonucleotide typing reveals association of type I psoriasis with the HLA-DRB1*0701/2, -DQA1*0201, -DQB1*0303 extended haplotype. *J Invest Dermatol* 100:749, 1993
23. Trembath RC et al: Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. *Hum Mol Genet* 6:813, 1997
24. Henseler T, Christophers E: Disease concomitance in psoriasis. *J Am Acad Dermatol* 32:982, 1995
25. Stern R et al: Psoriasis and the risk of cancer. *J Invest Dermatol* 78:147, 1982
26. Stern RS et al: Cutaneous squamous cell carcinomas in patients treated with PUVA. *N Engl J Med* 310:1156, 1984
27. Christophers E, Henseler T: Contrasting disease patterns in psoriasis and atopic dermatitis. *Arch Dermatol Res* 279:S48, 1987
28. Aly R et al: Bacterial flora in psoriasis. *Br J Dermatol* 95:603, 1976
29. Van Scott EJ, Ekel TM: Kinetics of hyperplasia in psoriasis. *Arch Dermatol* 88:373, 1963
30. Uyemura K et al: The cytokine network in lesional and lesion-free psoriatic skin is characterized by a T-helper type 1 cell-mediated response. *J Invest Dermatol* 101:701, 1993
31. Schlaak JF et al: T cells involved in psoriasis vulgaris belong to the Th1 subset. *J Invest Dermatol* 102:145, 1994
32. Kägi MK et al: Differential cytokine profiles in peripheral blood lymphocyte supernatants and skin biopsies from patients with different forms of atopic dermatitis, psoriasis and normal individuals. *Int Arch Allergy Immunol* 103:332, 1994
33. Lewis HM et al: Restricted T-cell receptor V β gene usage in the skin of patients with guttate and chronic plaque psoriasis. *Br J Dermatol* 129:514, 1993
34. Menssen A et al: Evidence for an antigen-specific cellular immune response in skin lesions of patients with psoriasis vulgaris. *J Immunol* 155:4078, 1995
35. Chang JCC et al: CD8+ T cells in psoriatic lesions preferentially use T cell receptor V β 3 and/or V β 13.1 genes. *Proc Natl Acad Sci USA* 91:9282, 1994
36. Boehncke W-H et al: T-cell-receptor repertoire in chronic plaque-stage psoriasis is restricted and lacks enrichment of superantigen-associated V β regions. *J Invest Dermatol* 104:725, 1995
37. Babi LFS et al: Migration of skin-homing T cells across cytokine-activated human endothelial cell layers involves interaction of the cutaneous lymphocyte-associated antigen (CLA), the very late antigen-4 (VLA-4), and the lymphocyte function-associated antigen-1 (LFA-1). *J Immunol* 154:1543, 1995
38. Vallat VP et al: PUVA bath therapy strongly suppresses immunological and epidermal activation in psoriasis: A possible cellular basis for remittive therapy. *J Exp Med* 180:283, 1994
39. Krueger JG et al: Successful ultraviolet B treatment of psoriasis is accompanied by a reversal of keratinocyte pathology and by selective depletion of intraepidermal T cells. *J Exp Med* 182:2057, 1996
40. Eedy DJ et al: Clearance of severe psoriasis after allogeneic bone marrow transplantation. *BMJ* 300:908, 1990
41. Gardembas-Pain M et al: Psoriasis after allogeneic bone marrow transplantation. *Arch Dermatol* 126:1523, 1991
42. Picker LJ et al: Differential expression of homing-associated adhesion molecules by T cell subsets in man. *J Immunol* 145:3247, 1990
43. Gearing AJH et al: Cytokines in skin lesions of psoriasis. *Cytokine* 2:68, 1990
44. Fraki JE et al: Correlation of epidermal plasminogen activator activity with disease activity in psoriasis. *Br J Dermatol* 108:39, 1983
45. Fraki JE et al: Uninvolved skin from psoriatic patients develops signs of involved psoriatic skin after being grafted onto nude mice. *Science* 215:685, 1982
46. Wiedow O et al: An elastase-specific inhibitor of human skin. *J Biol Chem* 265:1491, 1990
47. Al Suwaidan SN, Feldman SR: Clearance is not a realistic expectation of psoriasis treatment. *J Am Acad Dermatol* 42:796, 2000
48. Schmidt KN et al: Anti-psoriatic drug anthralin activates transcription factor NF- κ B in murine keratinocytes. *J Immunol* 156:4514, 1996
49. Morimoto S et al: An open study of vitamin D $_3$ treatment in psoriasis vulgaris. *Br J Dermatol* 115:421, 1986
50. Kragballe K et al: Long-term efficacy and tolerability of topical calcipotriol in psoriasis. *Acta Derm Venereol (Stockh)* 71:475, 1991
51. Gerritsen MJP et al: The effect of tacalcitol [1,24(OH) $_2$ D $_3$] on cutaneous inflammation, epidermal proliferation and keratinization in psoriasis: A placebo-controlled, double-blind study. *Br J Dermatol* 131:57, 1994
52. Gerritsen MJ et al: Long-term safety of topical calcitriol 3 μ g/g ointment. *Br J Dermatol* 144(suppl 58):17, 2001
53. Van de Kerkhof PCM: Biological activity of vitamin D analogues in the skin, with special reference to antipsoriatic mechanisms. *Br J Dermatol* 132:675, 1995
54. Yu X-P et al: Down-regulation of NF-kappa B protein levels in activated human lymphocytes by 1,25-dihydroxyvitamin D $_3$. *Proc Natl Acad Sci USA* 92:10990, 1995
55. Penna G, Adorini L: 1 α , 25-dihydroxyvitamin D $_3$ inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *J Immunol* 164:2405, 2000
56. Oranje AP et al: Topical calcipotriol in childhood psoriasis. *J Am Acad Dermatol* 36:203, 1997
57. Koo JY: Tazarotene in combination with phototherapy. *J Am Acad Dermatol* 39:S144, 1998
58. Parrish JA et al: Photochemotherapy of psoriasis with oral methoxsalen and long-wave ultraviolet light. *N Engl J Med* 291:1207, 1974
59. Henseler T et al: Oral 8-methoxypsoralen photochemotherapy of psoriasis. European PUVA Study: A cooperative study among 18 European centres. *Lancet* 1:853, 1981
60. Pathak MA et al: Photobiology and photochemistry of furocoumarins (psoralens), in *Sunlight and Man: Normal and Abnormal Photobiologic Responses*, edited by MA Pathak, TB Fitzpatrick. Tokyo, Tokyo University Press, 1974, p 25
61. Stern RS et al: Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). *N Engl J Med* 336:1041, 1997
62. Fischer T, Alsins J: Treatment of psoriasis with trioxsalen baths and dysprosium lamps. *Acta Derm Venereol (Stockh)* 56:383, 1976
63. Stern RS, Lange R: Non-melanoma skin cancer occurring in patients treated with PUVA five to ten years after first treatment. *J Invest Dermatol* 91:120, 1988
64. Streit V et al: Treatment of psoriasis with polyethylene sheet bath PUVA. *J Am Acad Dermatol* 35:208, 1996
65. Abels DJ, Kattan-Byron J: Psoriasis treatment at the Dead Sea: A natural selective ultraviolet phototherapy. *J Am Acad Dermatol* 12:639, 1985
66. Jeffes EWB III et al: Methotrexate therapy of psoriasis: Differential sensitivity of proliferating lymphoid and epithelial cells to the cytotoxic and growth-inhibitory effects of methotrexate. *J Invest Dermatol* 104:83, 1995
67. Genestier L et al: Immunosuppressive properties of methotrexate: Apoptosis and clonal deletion of activated peripheral T cells. *J Clin Invest* 102:322, 1998
68. Heenen M et al: Methotrexate induces apoptotic cell death in human keratinocytes. *Arch Dermatol Res* 290:240, 1998
69. Zachariae H et al: The value of amino-terminal propeptide of type III procollagen in routine screening for methotrexate-induced liver fibrosis: A 10-year follow-up. *Br J Dermatol* 144:100, 2001
70. Hassan W: Methotrexate and liver toxicity: Role of surveillance liver biopsy. *Ann Rheum Dis* 55:273, 1996
71. Roenigk HH et al: Methotrexate in psoriasis: Consensus conference. *J Am Acad Dermatol* 38:478, 1998
72. Schreiber SL, Crabtree GR: The mechanism of action of cyclosporin A and FK506. *Immunol Today* 13:136, 1992
73. Mrowietz U et al: Long-term maintenance therapy with cyclosporine and post-treatment survey in severe psoriasis, results of a multicenter study. *J Am Acad Dermatol* 33:470, 1995
74. Marcil I, Stern RS: Squamous-cell cancer of the skin in patients given PUVA and cyclosporin: Nested cohort crossover study. *Lancet* 358:1042, 2001
75. Almond-Roesler B, Orfanos CE: *trans*-Acitretin is metabolized back to etretinate: Importance for oral retinoid therapy. *Hautarzt* 47:173, 1996
76. De Jong P et al: Selective stimulation of T helper 2 cytokine responses by the anti-psoriasis agent monomethylfumarate. *Eur J Immunol* 26:2067, 1996
77. Zhu K, Mrowietz U: Inhibition of dendritic cell differentiation by fumaric acid esters. *J Invest Dermatol* 116:203, 2001
78. Vandermeeren M et al: Dimethylfumarate is an inhibitor of cytokine-induced nuclear translocation of NF-kappa B1, but not RelA in normal human dermal fibroblast cells. *J Invest Dermatol* 116:124, 2001
79. Stoof TJ et al: The antipsoriatic drug dimethylfumarate strongly suppresses chemokine production in human keratinocytes and peripheral blood mononuclear cells. *Br J Dermatol* 144:1114, 2001
80. Mrowietz U et al: Treatment of severe psoriasis with fumaric acid esters: Scientific background and guidelines for therapeutic use. *Br J Dermatol* 141:424, 1999
81. Altmeyer P et al: Antipsoriatic effect of fumaric acid derivatives: Results of a multicenter double-blind study in 100 patients. *J Am Acad Dermatol* 30:977, 1994

CHAPTER 43

Robert Winchester

Psoriatic Arthritis

DEFINITION AND CLASSIFICATION

Psoriatic arthritis is a CD8 T cell-driven autoimmune inflammation that affects the ligaments, tendons, fascia, and spinal or peripheral joints in persons with psoriasis. The pathologic processes in psoriatic arthritis exhibit many parallels to processes found in the skin lesions. Psoriatic arthritis is recognized in about 10 percent of individuals with well-established psoriasis. However in 10 to 15 percent of those with psoriatic arthritis, either the arthritis appears synchronously with the first evidence of skin disease, or no cutaneous involvement is ever detected. In parallel with the skin disease, psoriatic arthritis is exacerbated by physical stress, nonspecific inflammation, or certain infections. Unlike most autoimmune diseases, psoriatic arthritis increases in prevalence and severity in those with advancing AIDS, and special concerns exist about its therapy in this setting.

Psoriatic arthritis is a prototypic major histocompatibility gene complex (MHC) class I-associated autoimmune form of arthritis, in which genetic susceptibility is provided by the MHC class I allele HLA-B27, and additional class I alleles, including those implicated in psoriasis susceptibility. Psoriatic arthritis is classified as one of the seronegative spondyloarthritis group of disorders that includes ankylosing spondylitis, undifferentiated spondylitis, Reiter's syndrome, reactive arthritis, and enteropathic arthritis. These disorders share involvement of the spine (spondylo) and sacroiliac joints and some degree of genetic susceptibility associated with HLA-B27. In particular, many features of the pathogenesis of psoriatic arthritis, including the importance of CD8 T cells, are similar to those of Reiter's syndrome/reactive arthritis and are highly distinct from features of rheumatoid arthritis. The older term "spondyloarthropathy" is falling from use as evidence of the importance of inflammation increases. In addition to synovitis, the spondyloarthritis group of disorders has the singularly distinctive feature of

89. Asadullah K et al: IL-10 is a key cytokine in psoriasis. Proof of principle by IL-10 therapy: A new therapeutic approach. *J Clin Invest* 101:783, 1998
90. Reich K et al: Response of psoriasis to interleukin-10 is associated with suppression of cutaneous type 1 inflammation, downregulation of the epidermal interleukin-8/CXCR2 pathway and normalization of keratinocyte maturation. *J Invest Dermatol* 116:319, 2001
91. Mrowietz U et al: The novel ascomycin derivative SDZ ASM 981 is an effective anti-psoriatic compound when used topically under occlusion. *Br J Dermatol* 139:992, 1998
92. Zonneveld IM et al: Topical tacrolimus is not effective in chronic plaque psoriasis: A pilot study. *Arch Dermatol* 134:1101, 1998
93. Asawanonda P et al: 308-nm excimer laser for the treatment of psoriasis: A dose-response study. *Arch Dermatol* 136:619, 2000

inflammation involving the periarticular structures, particularly tendons and ligaments at their respective points of insertion, which is termed *enthesitis*. This condition results in tendinitis, dactylitis (sometimes graphically termed "sausage digits"), and fasciitis.

Psoriatic arthritis is distinguished from the other spondyloarthritides, such as ankylosing spondylitis, by the limited extent and frequency of spinal involvement, the predominance of peripheral joint involvement, and the relationship to psoriasis. The peripheral joints are involved in a variety of patterns at presentation (Table 43-1), and these patterns are often useful diagnostically as emphasized by Moll and Wright in their classic paper.¹ Indeed, distal interphalangeal joint involvement in an individual with psoriasis is a pattern of joint disease

TABLE 43-1

Patterns of Psoriatic Arthritis

Asymmetric or symmetric peripheral joint involvement

- Distal interphalangeal joint involvement
- Small joints of hands and feet
- Large joints, primarily of legs
- Combination of above (erosive arthritis without osteopenia)

Axial disease

- Spine and sacroiliac joints, with or without peripheral joint involvement

Associated Features

- Tenosynovitis
- Enthesitis
- Onychodystrophy, especially with distal interphalangeal joint involvement
- New bone formation (vertebral squaring, entheses)
- Joint fibrosis and ankylosis
- Osteolysis and mutilating arthritis

that immediately suggests the diagnosis of psoriatic arthritis. However, these patterns are not stable. Over time the disease follows one of two principal patterns of joint involvement: (1) predominant axial disease, the less common form consisting of sacroiliitis with or without peripheral arthritis, and (2) the more common form of peripheral disease without sacroiliitis.²

HISTORIC ASPECTS

The identification of psoriatic arthritis in skeletal remains of individuals who sought refuge in ancient Middle Eastern Byzantine monasteries suggests that psoriasis with psoriatic arthritis was one of the forms of biblical "leprosy," attesting to the severe and ancient nature of this condition.³ The association of arthritis with psoriasis was first formally described in 1818 by Alibert, and was designated psoriasis arthritique by Bazin in 1860. The notion of a distinctive arthritis associated with psoriasis became widely accepted,^{4,5} but after World War II psoriatic arthritis was grouped with rheumatoid arthritis as a "rheumatoid variant" or "rheumatoid spondylitis." Subsequently, the distinct nature of psoriatic arthritis was again emphasized, using as criteria the absence of rheumatoid factor and the presence of HLA-B27, enthesitis, and spondylitis.⁶⁻⁸ Furthermore, whereas rheumatoid arthritis commonly regresses with advancing HIV infection, psoriatic arthritis becomes more prevalent and intense.⁹⁻¹¹

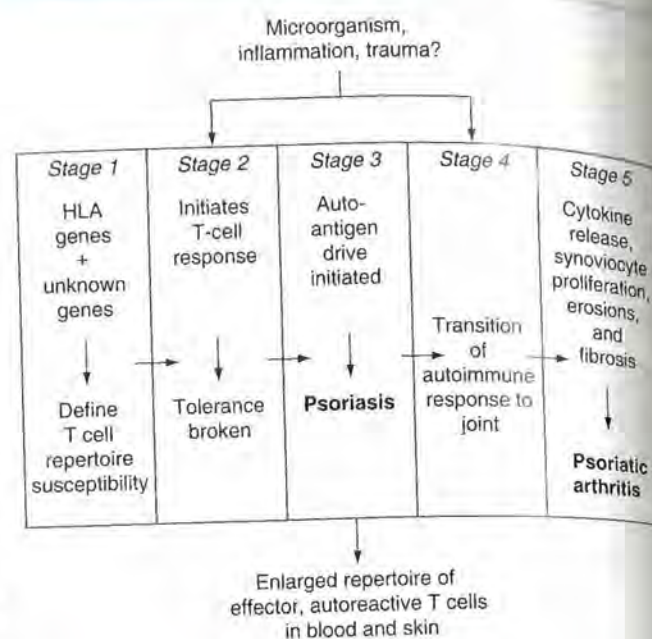
EPIDEMIOLOGY

Psoriatic arthritis is found in just under 10 percent of individuals with psoriasis,^{12,13} but some series report a much higher prevalence that could reflect in part the absence of sensitive and fully developed criteria for diagnosing joint involvement.¹⁴ If the frequency of psoriasis is between 1 and 3 percent, the prevalence of psoriatic arthritis in the general Caucasian population, according to current criteria, would be from 0.05 to 0.24 percent, a value approaching half that of the prevalence of seropositive rheumatoid arthritis and in agreement with recent prevalence studies.¹⁵ A critical review of the syndromic criteria used to diagnose psoriatic arthritis emphasized that all currently used classification/diagnosis criteria have a high specificity but low sensitivity, including those of Moll and Wright, the European Spondyloarthropathy Study Group, and the Amor classification criteria.¹⁵ Importantly, criteria with low sensitivity fail to provide sufficient guidance to the physician for patient diagnosis.

A MODEL OF THE STAGES OF DISEASE PATHOGENESIS

In common with other autoimmune diseases, psoriasis and, subsequently, psoriatic arthritis can be considered to develop in stages, beginning with genetically defined predisposition and ending with overt joint disease (Fig. 43-1). The following sections describe in some detail the stages in the pathogenesis of psoriatic arthritis.

FIGURE 43-1



Hypothetical stages in the development of psoriasis or psoriatic arthritis. The first stage is one of genetically defined susceptibility. MHC class I molecules, self-peptides, and other, still unknown genes interact to select a T cell repertoire that has the property of recognizing a self-peptide critical to the pathogenesis of psoriasis or psoriatic arthritis. The second compartment depicts several possible initiation events where the T cell clones, selected in stage one are triggered to recognize a self-peptide. This physiologic adaptive immune response is initiated by a specific microorganism or by nonantigen-specific inflammation or trauma. In the third stage, the unlimited amount of self-peptide autoantigen drives the immune response to clonal expansion and an effector phenotype that results in psoriasis. In the fourth stage, these T cell clones acquire the ability to respond to a self-antigen of the joint. In the final stage, these clones acquire the potential to injure the joint by the release of chemokines that recruit and activate monocytes and nonantigen-specific T cells. Multiple inflammatory mechanisms characterize this stage.

Stage One: Genetic Factors Defining Predisposition

Typically, the predisposition phase lasts two or more decades. Germ-line genes contribute in an important way to the definition of the predisposition to develop psoriasis and psoriatic arthritis, as is shown by the strong familial aggregation of psoriatic arthritis and high twin concordance rates.¹⁶ Psoriatic arthritis or psoriasis was found in 40 percent of first-degree relatives of those with the same disease,¹⁷ a likelihood forty-fold greater than that of their unaffected spouses.^{6,18,19} The ratio of familial psoriatic arthritis prevalence to its population prevalence (λ_r) is 20 to 30, being much greater than that for rheumatoid arthritis. Some relatives of a psoriatic arthritis proband may exhibit only typical psoriasis; others may have only an atypical undifferentiated spondyloarthritis; and still others may exhibit classic psoriatic arthritis and psoriasis.¹⁸

The inheritance of psoriatic arthritis has a mixed pattern found in many autoimmune diseases that either simulates a partially dominant mode of inheritance that is incompletely penetrant¹ or fits a recessive mode.²⁰ The concordance rate for psoriatic arthritis in both members of an identical twinning is 30 to 40 percent,¹⁶ suggesting that only a third of those with a genetic predisposition actually develop psoriatic arthritis. This finding suggests that the development of psoriatic arthritis depends on nongerm-line-encoded events that could be environmental, involving infection or trauma,²¹ or stochastic factors such as T cell repertoire development.

HLA CLASS I GENES INVOLVED IN DETERMINING SUSCEPTIBILITY

The first report of a specific allele marking susceptibility to psoriatic arthritis was by Brewerton et al.,⁸ who identified a HLA-B27 allele in approximately 20 percent of patients with the peripheral joint involvement of psoriatic arthritis. In addition, the influence of immunogenetic factors on the pattern of joint involvement in psoriatic arthritis was shown by an increase of the frequency of HLA-B27 to approximately 70 percent in patients with spine involvement. These studies have been widely confirmed.^{2,19,22} In some populations, additional rare class I alleles, such as HLA-B38 and HLA-B39, are associated with psoriatic arthritis,²³ but not with psoriasis. These alleles appear to be functional alternatives to HLA-B27 in terms of analogous peptide-binding properties, but they do not share ancestral haplotypes with HLA-B27 alleles.

Other class I MHC alleles also have been implicated, including HLA-B13 and HLA-B57. These alleles sharply distinguish psoriatic arthritis from the other spondyloarthritides that do not exhibit any associations of susceptibility with them. The allele group characterized by HLA-Cw6 is found in strong linkage disequilibrium with both HLA-B57 and HLA-B13, but not with HLA-B27, HLA-B38, or HLA-B39; this observation provides the first molecular evidence of potential genetic heterogeneity in psoriatic arthritis (see Chaps. 24 and 42). HLA-Cw6 is present in well over half of all persons with psoriatic arthritis in some studies.^{23,24} Alleles encoding HLA-B13 and HLA-B57 are also in strong linkage disequilibrium with the HLA-DR7 and the DQA1*0201 alleles, emphasizing the large genomic distances over which ancestral haplotypes extend. HLA-DR7 and the DQA1*0201 alleles have also been reported at increased frequency in psoriatic arthritis and psoriasis.^{25,26} A recent study suggests that the major region determining susceptibility to psoriatic arthritis is centromeric of the HLA-B locus.²⁷

At this time, the most probable interpretation of the association of HLA-B27 and the second group of HLA class I alleles, including HLA-B13, HLA-B57, and HLA-Cw6, with the susceptibility to develop psoriasis or psoriatic arthritis, is that these HLA molecules act to select a particular repertoire of CD8 T cells by binding and presenting certain self-peptides during the phase of positive thymic selection of the T cell repertoire. The presence of a T cell repertoire containing clones that can react with a particular self-peptide is a necessary but insufficient condition for psoriatic arthritis.

Stage Two: Triggering of Self-Tolerant T Cells

The second stage of the disease is activation of one or a few clones of CD8 T cells directed to a self-antigen in what is the first part of an adaptive immune response. If tolerization to self in the negative selection phase of repertoire formation were efficient, it would remove all the clones produced in the positive selection phase, because these were all selected on self-peptides. The individuals with psoriatic susceptibility alleles are left with potentially self-reactive CD8 T cells in their repertoire. In some instances, the clone may be in a state termed *clonal ignorance* rather than tolerance, because the provision of appropriate costimulatory signals to the T cells by accessory molecules will result in the response of the T cell clone. The events that trigger the CD8 T cells to become autoreactive are unknown.

Stage Three: Clonal Expansion and the Development of Psoriasis

The third phase of the immunopathogenesis of the immune response leading up to clinical skin disease consists of further substantive CD8 T cell clonal expansion and differentiation to an effector phenotype driven by psoriatic self antigens, as depicted in the third compartment in Fig. 43-1. Typically, the phase of psoriasis without joint involvement

lasts nearly another decade until the phase of overt arthritis is precipitated. Detailed aspects of this adaptive immune response are covered in Chap. 42. Ultimately, the number of effector T cell clones with the requisite specificities accumulates to a level capable of initiating a disease-inducing autoimmune response to dermal keratinocytes.

Stage Four: Transition of the Autoimmune Response to the Joint

In a subset of individuals with psoriasis, the autoimmune response advances to involve the joint in what appears to be a similar disease process. There are two alternative possibilities. The autoimmune response affecting the joint is identical to that affecting the skin in terms of peptide recognition, or there is an additional joint-specific immune response that recognizes a peptide distinct from that recognized in keratinocytes. In either case, the development of joint inflammation appears to require a large pool of expanded antigen-reactive CD8 T cell clones with an effector cell phenotype.

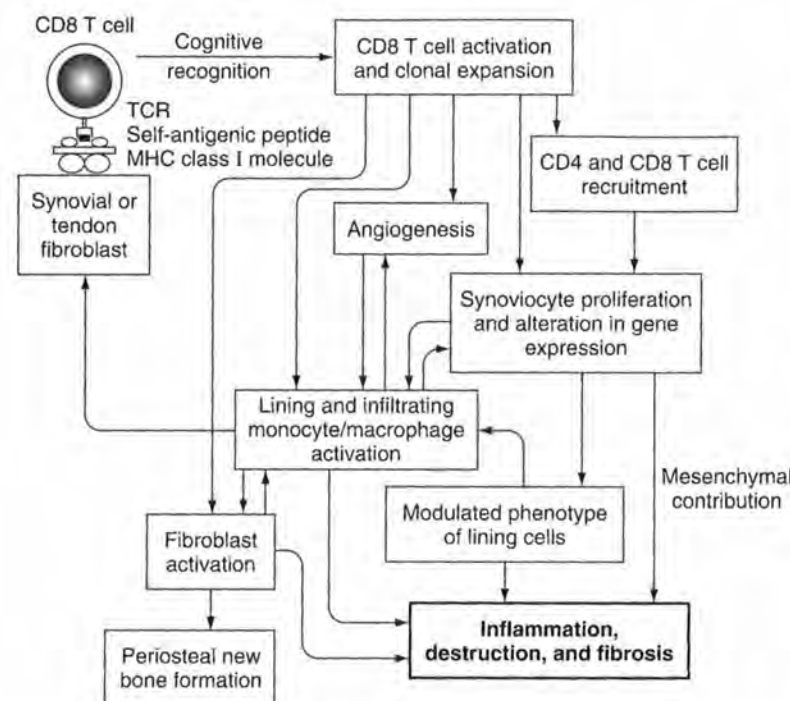
Stage Five: Development of Joint Inflammation and Injury

A model for sustained immune stimulation responsible for stage five (Fig. 43-2) envisions a CD8 T cell that cognitively recognizes the specific self-peptide responsible for psoriasis and psoriatic arthritis and responds with activation and proliferation, which drive the inflammatory response responsible for joint inflammation and destruction. A cascade of secondary immune responses occurs in the joint tissue as a result of this drive. Chemokines and cytokines released by this activation (see Chaps. 26 and 27), act on vascular endothelium and monocyte macrophages to affect their pattern of gene expression, and also instigate the nonantigen-specific recruitment of other CD8 T cells and CD4 T cells into the site of inflammation, as well as additional monocytes. These recruited bystander cells, in turn, release additional cytokines that act on synovial lining cells and other cells in the fibroblast lineage to alter their pattern of gene expression, proliferate, and induce new bone formation, in a manner similar to that postulated for their effect on keratinocytes in psoriatic plaques.²⁸ The combination of cytokines, chemokines, and other proinflammatory factors from these cell types results in joint and tendon inflammation, destruction, and fibrosis.

NATURE OF THE INFLAMMATORY INFILTRATE IN FULLY DEVELOPED PSORIATIC ARTHRITIS

The striking feature in the synovium and joint fluid of patients with psoriatic arthritis is the presence of a small number of very large CD8 T cell clonal expansions with structural features that strongly imply they result from an autoantigen drive.^{29,30} These form groups of structurally related clones with the same CDR3 length and the same or homologous CDR3 amino acid sequences. The CD8 T cell clones are derived from an effector precursor pool that is highly expanded in blood (> 20 cell divisions) and could be the population involved in mediating the skin disease. These cells appear to be the CD8 T cells originally selected in the predisposition phase, and they now drive the psoriatic inflammatory process in an autoantigen-driven adaptive immune response (Fig. 43-2). The activation of these cells and their release of chemokines and cytokines are considered to be the basis of the arthritis and enthesitis.

FIGURE 43-2



Scheme for pathogenesis of inflammation and tissue destruction in psoriatic arthritis. The process is driven by cognitive recognition of a self-peptide presented to a CD8 T cell by a MHC class I molecule on a joint cell. The ensuing T cell activation and clonal expansion initiates nonantigen-specific recruitment of CD4 and CD8 T cells, angiogenesis, and monocyte recruitment and activation by the release of cytokines and chemokines. The activated cells, in turn, alter patterns of gene expression in cells comprising the joint and related structures. These alterations result in inflammation, fibrosis, new bone formation, erosions, and osteolysis.

The synovium in active arthritis also contains a preponderant infiltrate of polyclonal, nonantigen-specific CD4 T cells (Fig. 43-3), as shown by analysis of the T cell receptor (TCR) β chain (V_{β}) repertoire at a molecular level.^{29,30} These nonantigen-specific T cells arise via recruitment mediated by chemokines, such as monocyte chemoattractant protein 1 (MCP-1), which is locally produced in the synovium.³¹ Cytokines implicated in the pathogenic process of psoriatic arthritis include interleukin (IL)-6, IL-1 β , IL-2, and sIL-2R.³² T cells in infiltrates elaborate regulated on activation, normal T cell expressed and secreted (RANTES), while macrophages in the lining are gro- α positive, and those in infiltrates are Mig positive.³³ IL-8, a chemokine that could be responsible for the attraction of neutrophils to the joint fluid in psoriatic arthritis is expressed at a high level in the synovial lining cells, and to a lesser extent, in cells located in the perivascular areas. Compared with rheumatoid arthritis synovium, there is markedly less interferon- γ and IL-1 in the psoriatic arthritis synovium. This finding is consistent with the lack of a T_H1 pattern of cytokine production and the dominant role of CD8 T cells.³⁴ Vascular abnormalities are early histopathologic changes that occur in the psoriatic plaque and are also prominent in the psoriatic synovium; these changes are likely to reflect specific cytokine profiles augmented in the patient with psoriasis. The destruction of cartilage differs from that in rheumatoid arthritis by the presence of minimally elevated levels of aggrecan and greatly increased concentrations of cartilage oligomeric matrix protein.³⁵

Other types of bystander-type clonal expansions found in joint fluid are directed to diverse viral and other antigens unrelated to the presumed autoantigens driving the joint disease. These are presumably attracted to the inflammatory milieu and may secondarily contribute to the intensification of arthritis.

The mode of action of methotrexate on the inflammatory T cell infiltrate was recently elucidated by characterization of the T cell repertoire in synovial biopsies of methotrexate-treated patients with full drug-induced remissions.³⁰ The polyclonal infiltration of predominantly CD4 T cells that dominates the synovium in acute arthritis largely disappears, but the CD8 antigen-driven oligoclonal expansions identified by their sequence remained largely undiminished over 12 to 18 months of therapy. The inability of methotrexate therapy to eliminate the expanded CD8 clones suggests that the methotrexate is suppressive rather than curative. It appears that tumor necrosis factor (TNF) blockade therapy also eliminates major components of the effector pathways of joint inflammation, without significantly altering the lymphocyte populations underlying the autoimmune drive of psoriatic arthritis.³⁶ Reductions were noted in lining layer thickness, vascularity, and infiltration with neutrophils and macrophages that paralleled the beneficial effect of anti-TNF- α therapy. It is likely that anti-TNF agents exert their beneficial effect largely, if not solely, on the later parts of the inflammatory cascade shown in Fig. 43-2.

CLINICAL MANIFESTATIONS

Onset and Occurrence

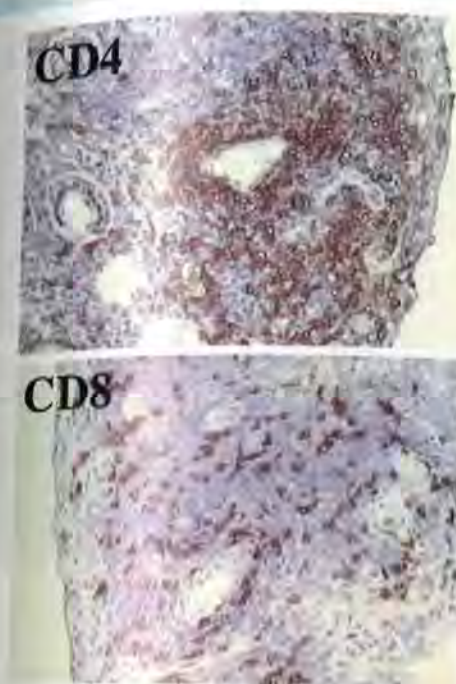
Psoriatic arthritis characteristically develops between ages 35 and 45, an average of 10 years after the appearance of psoriasis, but can occur at nearly any age. Onset earlier in adulthood or in childhood is associated with a heightened likelihood of developing destructive arthritis. Typically, early onset psoriatic arthritis occurs in a setting of a strong family history of the disease.¹⁷ The sex ratio parallels that of psoriasis, with a preponderance of females in early childhood, but an essentially equivalent incidence in both sexes in adults.

The onset of arthritis is usually insidious, but occasionally is abrupt, sometimes following a joint injury. In these latter cases, the intensity of the disease may suggest Reiter's syndrome or gout. The subsequent course of posttraumatic psoriatic arthritis is indistinguishable from that of spontaneous onset arthritis.³⁷ Pitting edema of the hands or feet, sometimes asymmetric, secondary to enthesitis and tenosynovitis has been reported as a first, isolated manifestation of psoriatic arthritis.³⁸ The development of insidious inflammatory back pain is an important clue to the recognition of axial disease, and this symptom may be the initial manifestation of psoriatic arthritis (Table 43-2). Constitutional features, including fever and malaise, are uncommon and usually are evident only in a fulminant onset with widespread joint disease. However, the erythrocyte sedimentation rate and the serum complement level are commonly elevated, reflecting activation of acute phase reactants by cytokines.¹⁹

Skin Disease

Susceptibility to the development and severity of arthritis generally increases with the severity of cutaneous involvement. However, remissions and exacerbations of the joint disease correlate poorly with similar changes in the skin disease.¹²

FIGURE 43-3



Inflammatory infiltrate of active synovitis in psoriatic arthritis, showing the predominant infiltration of CD4 T cells and somewhat fewer CD8 T cells. (Courtesy of D. Kane.)

Joint Disease Patterns and Radiology

The pattern of peripheral joint involvement² and the associated findings of nail disease, tenosynovitis, enthesitis, ankylosis, periosteal new bone formation, erosions, osteolysis, and axial involvement provide hallmarks for the recognition of psoriatic arthritis at the bedside and through radiology (Table 43-1; Fig. 43-4). Approximately three-fourths of persons diagnosed with psoriatic arthritis manifest peripheral, usually asymmetric, oligoarthritis that involves the small joints of the hands and feet, the large joints of the legs, or a combination of both small and large joints. When only a few joints are involved, the distribution appears asymmetric. The hand involvement can include stiffness and dactylitis that are attributable to enthesitis as well as synovitis. Dactylitis is strongly suggestive of psoriatic arthritis when it occurs in an individual with psoriasis.³⁹ Deformity secondary to fibrosis and contractures may occur. The classic pencil-in-cup joint is sometimes seen, consisting of symmetric and conical osteolysis of the proximal head, with enlargement of the base of the distal head by new bone formation. Acral osteolysis and erosions at the tip of the tuft of the digit are characteristic, especially when they involve the hallux. Ankylosis of one or more isolated joints is another distinctive feature due to fibrosis

TABLE 43-2

Inflammatory Back Pain from Spondylitis, Sacroiliitis, or Axial Enthesitis as Initial Manifestation of Psoriatic Arthritis

- Onset before age 40
- Insidious dull, deep buttock or low back pain
- Poorly localized; does not follow nerve root
- Persists > 3 months
- Stiffness/pain on arising in the morning or during sleep
- Improvement with exercise
- Differential diagnosis from mechanical or degenerative spine disease

and new bone formation. Sometimes the initial or only manifestation of psoriatic arthritis is hallux rigidus, implying the subtle nature of joint inflammation and the need for its earlier recognition.

Inflammation of one or many of the distal interphalangeal joints is virtually pathognomonic for psoriatic arthritis or Reiter's syndrome; it need only be distinguished from Heberden's nodes, which occur in a form of osteoarthritis infection, or crystalline arthritides such as gout. In addition to the points of distinction summarized in Table 43-3, the distal interphalangeal joint is rarely, if ever, affected by rheumatoid arthritis. Typically, nail involvement is marked in the digit affected with arthritis, and there may be additional evidence of acral keratodystrophy.

The large joints that are affected in psoriatic arthritis include the hips, knees, and ankles. Often only a single hip or knee joint is involved; the dominant diagnostic considerations in adults include degenerative osteoarthritis or posttraumatic arthritis rather than psoriatic arthritis. Posttraumatic forms of psoriatic arthritis in athletes are particularly challenging to distinguish from purely mechanical injuries. In approximately 5 percent of persons with psoriatic arthritis, the character of the joint injury becomes profoundly destructive with marked osteolysis, resulting in what is sometimes referred to as *arthritis mutilans*. In rare instances this process is generalized, but much more commonly one or a few joints are characterized by destruction out of proportion to the remainder of the illness. Pustular psoriasis or erythroderma is more common among this group.⁴⁰

In occasional patients the sternomanubrial and temporomandibular joints may become involved, in association with extensive typical psoriatic arthritis. Certain syndromes simulate psoriatic arthritis but increasingly appear to be distinct entities; these include the anterior chest wall syndrome of sternomanubrial or costoclavicular involvement, where sternomanubrial disease occurs in isolation; the so-called SAPHO syndrome; and recurrent multifocal osteomyelitis. See reference 41 for a brief review of these entities.

Axial involvement is often most evident in the lower spine and sacroiliac joints. The predisposition to axial involvement is strongly influenced by the presence of HLA-B27. Scattered submarginal syndesmophytes and apophyseal or odontoid erosions without vertebral squaring or ligamentous calcification are found. Sometimes the non-marginal syndesmophytes become bulky, broad paravertebral excrescences that contrast with the vertically oriented outgrowths of bone in the outer margins of the annulus fibrosus in ankylosing spondylitis.^{42,43} Vertebral squaring from new bone formation, apophyseal joint involvement, and ligamentous calcification in the lumbar spine are similar to those found in ankylosing spondylitis. Asymmetric or symmetric sacroiliitis is frequent and is readily identified by computed tomography (CT) or magnetic resonance (MR) imaging. Symphysisitis is also present. CT and MR imaging are far more sensitive and specific than conventional x-rays for demonstrating sacroiliitis.⁴⁴ By directly imaging changes in the synovium, articular cartilage, and subchondral bone, MR imaging is the most sensitive and specific technique for detecting sacroiliitis and other changes in the axial skeleton.⁴⁴

Whether ascertainment of joint involvement by clinical and classic x-ray procedures in those with psoriasis is adequate has been the subject of several studies with newer imaging modalities such as radionuclide scanning, ultrasonography, and nuclear MR imaging. In a study using MR imaging to examine the frequency of hand involvement in patients with nummular and/or plaque psoriasis who did not have arthritic symptoms, Offidani et al.⁴⁵ found that 68 percent of patients with psoriasis had at least one arthritic sign, such as soft-tissue swelling, periarticular effusion, joint effusion-synovial pannus, tendon sheath effusion, bone erosion, subluxation, bone cysts, and subchondral signal intensity abnormalities; by contrast, standard x-rays revealed joint abnormalities in only 32 percent. The ability of magnetic resonance to image

Several biochemical families of NSAIDs or analgesics are available for therapy. Although these agents have some differences in anti-inflammatory efficacy and toxicity, choosing which NSAID to start is mainly dictated by physician experience and the individual response of a patient. Naproxen and indomethacin are traditionally considered representative of NSAIDs with the greatest efficacy in treating spondyloarthritides. Adverse effects shared by all NSAIDs include gastric and renal toxicity; hypersensitivity reactions; central nervous system effects, in particular tinnitus and headache; and coagulation abnormalities. In some patients with psoriasis, NSAIDs induce an idiosyncratic flare of the psoriatic skin lesions, possibly the result of the enhanced production of leukotrienes that occurs with cyclooxygenase inhibition. Most patients have had experience with self-prescribed drugs of this class; and before NSAID therapy is initiated, patients should be asked whether aspirin has caused a flare of psoriasis.

Lack of adequate response to NSAIDs or the presence of progressive or moderate to severe arthritis usually requires additional drug therapy. Intraarticular glucocorticoid injections may relieve an isolated episode of severe synovitis. Injections into the tendon sheaths, usually under ultrasound imaging, may be particularly effective in reducing enthesitis. Systemic glucocorticoid therapy should usually be avoided because of low efficacy coupled with the risks of inciting a transition to pustular psoriasis and a rebound of the skin disease on withdrawal. Sulfasalazine is helpful in reducing clinical parameters of joint disease activity in approximately 30 to 40 percent of patients in extensively documented double blind trials,⁶² especially in those with spondylitis.⁶³ Untoward reactions have been few, mainly a hypersensitivity dermatitis or gastrointestinal intolerance. Parenteral or oral gold salts are rarely used because of their limited efficacy.⁶²

Severe Destructive Arthritis

For the treatment of severe destructive arthritis, NSAIDs are supplemented with a more potent anti-inflammatory agent with immunomodulatory properties, such as methotrexate, cyclosporin A, or TNF blockers. The efficacy of both parenteral and, to a lesser degree, oral methotrexate has been extensively documented, and this drug is the current mainstay of therapy for severe arthritis.^{64,65} The better-documented efficacy of parenteral methotrexate suggests that this route of administration may be optimal for initial or maintenance therapy in instances of more severe disease.⁶² The side effects of methotrexate are discussed in Chaps. 42 and 256. Minimal immune impairment is sometimes encountered, and the uncommon possibility of developing opportunistic infections such as *Pneumocystis carinii* should be kept in mind in the differential diagnosis of pneumonitis developing during methotrexate therapy.

In view of the important role of TNF- α as an effector of inflammation in psoriatic arthritis, the anti-TNF agents etanercept and infliximab are taking a place in the therapy of severe destructive psoriatic arthritis, especially in individuals who do not respond to methotrexate.⁶⁶⁻⁶⁸ Parallel improvement in skin lesions usually occurs. In one 12-week trial, 73 percent of patients treated with etanercept given subcutaneously twice weekly exhibited an improvement in ACR20 as compared to 13 percent in the placebo group. This is a relatively modest response criteria set, but other less well-controlled studies indicate a greater joint response. Infliximab, administered intravenously at weeks 0, 2, and 6 resulted in marked improvement of arthritis and clearing of some histologic features of inflammation.³⁶ Considering the central role of TNF- α in the effector arm of the adaptive and innate immune response, blockade of this pathway will subtly impair immunity, as is reflected by instances of activation of latent *Mycobacterium tuberculosis* infection with therapy.⁶⁹ The evolving guidelines for use of these blockers should be consulted before therapy is considered. Attention to the de-

velopment of anti-DNA antibodies and other evidence of autoimmunity with therapy is also warranted.

Cyclosporin A improves both the skin and the joint disease in about 50 percent of patients treated with it. Improvement in skin disease occurs after 2 to 6 weeks of treatment, whereas joint disease took longer to improve.^{63,70} Within 4 weeks of discontinuing the drug, exacerbations of both skin and joint disease appeared. Untoward effects of cyclosporin A include usually reversible renal toxicity, with hypertension and azotemia, and the uncommon potential for the development of Epstein-Barr virus-related B cell lymphomas.

The place of DNA antimetabolites in the therapy of psoriatic arthritis has not received extensive analysis. Azathioprine was comparable in efficacy to methotrexate in a randomized trial.⁶² Mycophenolate mofetil was used in six patients with psoriatic arthritis with good results.⁷¹ A single report of the notable efficacy of 6-thioguanine in the treatment of psoriasis, associated with the depletion and induction of apoptosis in activated T lymphocytes, suggests that this compound may be beneficial in severe psoriatic arthritis as a complement to the mode of action of methotrexate and TNF blockade.⁷²

HIV Infection

In psoriatic arthritis associated with HIV infection, NSAIDs such as naproxen are the first line of therapy. However, in many patients, this drug does not adequately control inflammation, especially the very disabling enthesitis. Etretinate may be particularly useful in the treatment of this form of psoriatic arthritis because it lacks immunosuppressive effects.⁷³ Methotrexate, although effective in this setting, has been associated with the abrupt development of opportunistic infection and death in individuals with advanced HIV infection.¹⁰ Therefore, methotrexate and similar potentially immunosuppressive agents must be used with caution. Attention should be directed toward monitoring viral levels and overall immunologic competency during such therapy. The use of etanercept to treat psoriatic arthritis associated with HIV infection achieved an excellent clinical response of the skin and joint manifestations, but the drug had to be discontinued because of the development of multiple infections.⁷⁴ These observations emphasize the need for considering the presence of HIV infection when instituting immunosuppressive therapy in an individual with recent onset severe psoriatic arthritis.

Surgery and Related Techniques

Arthroscopic synovectomy or intraarticular injection of short-lived radioactive isotopes of elements such as ytterbium are experimental approaches that have been effective in treating instances of severe chronic monarticular synovitis. Because of the enhanced tendency to fibrosis associated with these therapies, anti-inflammatory and physical therapy measures aimed at improving range of motion are important adjuncts to these interventions. Joint replacement and forms of reconstructive therapy are appropriate in situations of advanced joint destruction. Anecdotal reports of the recurrence of psoriatic arthritis in the setting of a fully reconstituted donor marrow suggest that this approach, while promising for rheumatoid arthritis, is not likely to succeed in psoriatic arthritis.⁷⁵

REFERENCES

1. Moll JM, Wright V: Psoriatic arthritis. *Semin Arthritis Rheum* 3:55, 1973
2. Marsal S et al: Clinical, radiographic and HLA associations as markers for different patterns of psoriatic arthritis. *Rheumatology (Oxford)* 38:332, 1999
3. Zias J, Mitchell P: Psoriatic arthritis in a fifth-century Judean Desert monastery. *Am J Phys Anthropol* 101:491, 1996
4. Hench PS: Arthropathia psoriatica: Presentation of a case. *Proc Staff Meet Mayo Clin* 2:89, 1927

5. Bauer W et al: The pathology of joint lesions in patients with psoriasis and arthritis. *Trans Assoc Am Physicians* 56:349, 1941
6. Wright V: Psoriasis and arthritis. *Ann Rheum Dis* 15:348, 1956
7. Ball J: Enthesopathy of rheumatoid and ankylosing spondylitis. *Ann Rheum Dis* 30:213, 1971
8. Brewerton DA et al: HL-A 27 and arthropathies associated with ulcerative colitis and psoriasis. *Lancet* 1:956, 1974
9. Johnson TM et al: AIDS exacerbates psoriasis. *N Engl J Med* 313:1415, 1985
10. Winchester R et al: The co-occurrence of Reiter's syndrome and acquired immunodeficiency. *Ann Intern Med* 106:19, 1987
11. Winchester R et al: Implications from the occurrence of Reiter's syndrome and related disorders in association with advanced HIV infection. *Scand J Rheumatol* 74:89, 1988
12. Helligren L: Association between rheumatoid arthritis and psoriasis in total populations. *Acta Rheumatol Scand* 15:316, 1969
13. Shbeeb M et al: The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982. *J Rheumatol* 27:1247, 2000
14. Gladman DD, Brockbank J: Psoriatic arthritis. *Expert Opin Investig Drugs* 9:1511, 2000
15. Salvarani C et al: Psoriatic arthritis. *Curr Opin Rheumatol* 10:299, 1998
16. Gottlieb M et al: Discordance for psoriatic arthropathy in monozygotic twins. *Arthritis Rheum* 22:805, 1979
17. Rahman P et al: Comparison of clinical and immunogenetic features in familial versus sporadic psoriatic arthritis. *Clin Exp Rheumatol* 18:7, 2000
18. Moll JMH et al: Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies and Behçet's syndrome. *Medicine (Baltimore)* 53:343, 1974
19. Kammer GM et al: Psoriatic arthritis: A clinical, immunologic, and HLA study of 100 patients. *Semin Arthritis Rheum* 9:75, 1979
20. Swanbeck G et al: A population genetic study of psoriasis. *Br J Dermatol* 131:32, 1994
21. Moll JMH, Wright V: Familial occurrence of psoriatic arthritis. *Ann Rheum Dis* 22:181, 1973
22. Gerber LH et al: Human lymphocyte antigens characterizing psoriatic arthritis and its subtypes. *J Rheumatol* 9:703, 1982
23. Arnett FC, Bias WB: HLA-Bw38 and Bw39 in psoriatic arthritis: Relationships and implications for peripheral and axial involvement. *Arthritis Rheum* 23:649, 1980
24. Tiilikainen A et al: Psoriasis and HLA-Cw6. *Br J Dermatol* 102:179, 1980
25. Ikaheimo I et al: Immunogenetic profile of psoriasis vulgaris: Association with haplotypes A2, B13, Cw6, DR7, DQA1*0201 and A1, B17, Cw6, DR7, DQA1*0201. *Arch Dermatol Res* 288:63, 1996
26. Schmitt-Egenolf M et al: Familial juvenile onset psoriasis is associated with the human leukocyte antigen (HLA) class I side of the extended haplotype Cw6-B57-DRB1*0701-DQA1*0201-DQB1*0303: A population- and family-based study. *J Invest Dermatol* 106:711, 1996
27. Gonzalez S et al: Polymorphism in MICA rather than HLA-B/C genes is associated with psoriatic arthritis in the Jewish population. *Hum Immunol* 62:632, 2001
28. Grossman RM et al: Interleukin 6 is expressed in high levels in psoriatic skin and stimulated proliferation of cultured human keratinocytes. *Proc Natl Acad Sci USA* 86:6367, 1989
29. Costello PJ et al: Psoriatic arthritis joint fluids are characterized by CD8 and CD4 T cell clonal expansions appear antigen driven. *J Immunol* 166:2878, 2001
30. Curran SA et al: Psoriatic arthritis synovium is characterised by non-antigen-specific T cells that are selectively suppressed by methotrexate therapy. *Arthritis Rheumatol* 44:S235, 2001
31. Ross EL et al: Localized monocyte chemotactic protein-1 production correlates with T cell infiltration of synovium in patients with psoriatic arthritis. *J Rheumatol* 27:2432, 2000
32. Wong WM et al: Interleukin-2 is found in the synovium of psoriatic arthritis and spondyloarthritis, not in rheumatoid arthritis. *Scand J Rheumatol* 25:239, 1996
33. König A et al: Mig, GRO alpha and RANTES messenger RNA expression in lining layer, infiltrates and different leucocyte populations of synovial tissue from patients with rheumatoid arthritis, psoriatic arthritis and osteoarthritis. *Virchows Arch* 436:449, 2000
34. Canete JD et al: Differential Th1/Th2 cytokine patterns in chronic arthritis: Interferon gamma is highly expressed in synovium of rheumatoid arthritis compared with seronegative spondyloarthropathies. *Ann Rheum Dis* 59:263, 2000
35. Mansson B et al: Release of cartilage and bone macromolecules into synovial fluid: Differences between psoriatic arthritis and rheumatoid arthritis. *Ann Rheum Dis* 60:27, 2001
36. Baeten D et al: Immunomodulatory effects of anti-tumor necrosis factor alpha therapy on synovium in spondyloarthropathy: Histologic findings

- in eight patients from an open-label pilot study. *Arthritis Rheum* 44:186, 2001
37. Punzi L et al: Clinical, laboratory and immunogenetic aspects of post-traumatic psoriatic arthritis: A study of 25 patients. *Clin Exp Rheumatol* 16:277, 1998
38. Cantini F et al: Distal extremity swelling with pitting edema in psoriatic arthritis: A case-control study. *Clin Exp Rheumatol* 19:291, 2001
39. Rothschild BM et al: Dactylitis: Implications for clinical practice. *Semin Arthritis Rheum* 28:41, 1998
40. Koo T et al: Subsets in psoriatic arthritis formed by cluster analysis. *Clin Rheumatol* 20:36, 2001
41. Winchester R: Psoriatic arthritis and the spectrum of syndromes related to the SAPHO syndrome. *Curr Opin Rheumatol* 11:251, 1999
42. McEwen C et al: Ankylosing spondylitis and spondylitis accompanying ulcerative colitis, regional enteritis, psoriasis, and Reiter's disease. *Arthritis Rheum* 14:291, 1971
43. Jones MD et al: Bony overgrowths and abnormal calcifications about the spine. *Radiol Clin North Am* 26:1213, 1988
44. Luong AA, Salonen DC: Imaging of the seronegative spondyloarthropathies. *Curr Rheumatol Rep* 2:288, 2000
45. Offidani A et al: Subclinical joint involvement in psoriasis: Magnetic resonance imaging and x-ray findings. *Acta Derm Venereol* 78:463, 1998
46. Barozzi L et al: Seronegative spondyloarthropathies: Imaging of spondylitis, enthesitis and dactylitis. *Eur J Radiol* 27(suppl 1):S12, 1998
47. Taggart A, Wright V: Psoriatic arthritis, in *Epidermis: Disorders of Cell Kinetics and Differentiation*. 1990
48. Prieur AM, Chedeville G: Prognostic factors in juvenile idiopathic arthritis. *Curr Rheumatol Rep* 3:371, 2001
49. Shore A, Ansell BM: Juvenile psoriatic arthritis—An analysis of 60 cases. *J Pediatr* 100:529, 1982
50. Cabral DA et al: Visual prognosis in children with chronic anterior uveitis and arthritis. *J Rheumatol* 21:2370, 1994
51. Petty RE: Juvenile psoriatic arthritis, or juvenile arthritis with psoriasis? *Clin Exp Rheumatol* 12(suppl 10):S55, 1994
52. Robertson DM et al: Juvenile psoriatic arthritis: Followup and evaluation of diagnostic criteria. *J Rheumatol* 23:166, 1996
53. Kanakoudi-Tsakalidou F et al: Persistent or severe course of reactive arthritis following Salmonella enteritidis infection. A prospective study of 9 cases. *Scand J Rheumatol* 27:431, 1998
54. Reveille JD et al: Specific amino acid residues in the second hypervariable region of HLA-DQA1 and DQB1 chain genes promote the Ro (SS-A)/La (SS-B) autoantibody responses. *J Immunol* 146:3871, 1991
55. Duvic M et al: Acquired immunodeficiency syndrome associated psoriasis and Reiter's syndrome. *Arch Dermatol* 123:1622, 1987
56. Kaarela K et al: Work capacity of patients with inflammatory joint diseases. An eight-year follow-up study. *Scand J Rheumatol* 16:403, 1987
57. Gladman DD et al: Psoriatic arthritis (PSA)—An analysis of 220 patients. *QJM* 62:127, 1987
58. Coulton BL et al: Outcome in patients hospitalised for psoriatic arthritis. *Clin Rheum* 8:261, 1989
59. Husted JA et al: Health-related quality of life of patients with psoriatic arthritis: A comparison with patients with rheumatoid arthritis. *Arthritis Rheum* 45:151, 2001
60. Gladman DD et al: Remission in psoriatic arthritis. *J Rheumatol* 28:1045, 2001
61. Hanly JG et al: Psoriatic spondyloarthropathy: A long-term prospective study. *Ann Rheum Dis* 47:386, 1988
62. Jones G et al: Interventions for psoriatic arthritis. *Cochrane Database Syst Rev* 3, 2000
63. Salvarani C et al: A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol* 28:2274, 2001
64. Zachariae H, Zachariae E: Methotrexate treatment of psoriatic arthritis. *Acta Derm Venereol Suppl (Stockh)* 67:270, 1987
65. Steinsson K et al: Cyclosporin A in psoriatic arthritis: An open study. *Ann Rheum Dis* 49:603, 1990
66. Mease PJ et al: Etanercept in the treatment of psoriatic arthritis and psoriasis: A randomised trial. *Lancet* 356:385, 2000
67. Braun J et al: New treatment options in spondyloarthropathies: Increasing evidence for significant efficacy of anti-tumor necrosis factor therapy. *Curr Opin Rheumatol* 13:245, 2001
68. Ogilvie AL et al: Treatment of psoriatic arthritis with antitumor necrosis factor-alpha antibody clears skin lesions of psoriasis resistant to treatment with methotrexate. *Br J Dermatol* 144:587, 2001

69. Keane J et al: Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 345:1098, 2001
70. Mahrle G et al: Anti-inflammatory efficacy of low-dose cyclosporin A in psoriatic arthritis. A prospective multicentre study. *Br J Dermatol* 135:752, 1996
71. Grundmann-Kollmann M et al: Treatment of chronic plaque-stage psoriasis and psoriatic arthritis with mycophenolate mofetil. *J Am Acad Dermatol* 42:835, 2000

CHAPTER 44

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Exfoliative Dermatitis

Also referred to as erythroderma, exfoliative dermatitis is an inflammatory skin disease with erythema and scaling that affects nearly the entire cutaneous surface. It may be either primary (idiopathic) or secondary to a variety of drugs or underlying disorders. Primary exfoliative dermatitis has also been referred to as the "red man" or "l'homme rouge" syndrome. (See Chap. 138 for a discussion of exfoliative dermatitis associated with drugs; Chap. 157 for a discussion of exfoliative dermatitis associated with cutaneous T cell lymphoma.)

HISTORICAL ASPECTS

The classification of exfoliative dermatitis into Wilson-Brocq (chronic relapsing), Hebra or pityriasis rubra (progressive), and Savill (self-limited) types may have had historical value, but it currently lacks pathophysiologic or clinical utility.

EPIDEMIOLOGY

Exfoliative dermatitis is a rare, yet easily recognized, potentially serious skin condition. Its reported incidence varies widely: from 1 to 71 per 100,000 dermatologic outpatients.^{1,2,3} The higher incidences occurred in parts of Asia where the use of traditional medicaments by patients is common. A recent study in the Netherlands found an incidence of 0.9 patients per 100,000 inhabitants.⁴ In most case series, men outnumber women in a proportion of two to four men for every one woman, and the mean age is between 40 and 60 years.

ETIOLOGY AND PATHOGENESIS

Although a significant percentage of patients with exfoliative dermatitis have idiopathic disease (approximately 25 percent), the majority

72. Murphy FP et al: Clinical clearing of psoriasis by 6-thioguanine correlates with cutaneous T-cell depletion via apoptosis: evidence for selective effects on activated T lymphocytes. *Arch Dermatol* 135:1495, 1999
73. Louthrenoo W: Successful treatment of severe Reiter's syndrome associated with human immunodeficiency virus infection with etretinate. Report of 2 cases. *J Rheumatol* 20:1243, 1993
74. Aboulafia DM et al: Etanercept for the treatment of human immunodeficiency virus-associated psoriatic arthritis. *Mayo Clin Proc* 75:1093, 2000
75. Snowden JA et al: Long-term outcome of autoimmune disease following allogeneic bone marrow transplantation. *Arthritis Rheum* 41:453, 1998

of cases result from pre-existing skin diseases, in particular psoriasis (23 percent) and spongiotic disorders (16 percent), cutaneous T cell lymphoma (16 percent), and drug reactions (15 percent).¹⁻¹⁰ A survey of all dermatologists in the Netherlands indicated that, because practitioners refer only a minority of patients to academic centers, the number of idiopathic and malignancy-associated cases may be overestimated in many case series.⁴

The list of drugs that cause exfoliative dermatitis is large and continuously growing (Table 44-1). The association of most of these drugs with exfoliative dermatitis has come from isolated case reports with no clear dose-dependence, although it appears that antiepileptics, cimetidine, lithium, gold, allopurinol, quinidine, and calcium channel blockers may be particularly noteworthy as offending agents. However, it is important to consider all drug exposures, as intradermal and topical ocular preparations have been reported to induce exfoliative dermatitis.

A large number of systemic diseases, malignancies (hematologic or solid tumors), and infections may also play a role (Table 44-2). Exfoliative dermatitis may be the initial manifestation of HIV infection, although drug eruptions are the most common cause of exfoliative dermatitis in HIV-positive patients.¹¹ In infants with exfoliative dermatitis, seborrheic dermatitis, atopic dermatitis, psoriasis, and staphylococcal scalded skin syndrome are the most common causes. When the condition is congenital, however, the clinician should consider a variety of genetic disorders, in particular Netherton's syndrome and hereditary immunodeficiency syndromes.¹²

In most patients with pre-existing skin diseases, the exfoliative phase follows previous localized disease. For example, psoriatic exfoliative dermatitis can occur in association with the withdrawal of systemic or topical glucocorticoids, the use of systemic medications such as lithium and antimalarials, phototherapy burns, infection, pregnancy, and systemic illnesses in patients with previously limited psoriasis.

Regarding the pathogenesis of exfoliative dermatitis, it is not clear whether dermal inflammation or epidermal dysfunction is primary. Drug- and malignancy-induced exfoliative dermatitis suggests an inflammatory etiology, whereas exfoliative dermatitis in ichthyoses associated with transglutaminase mutations suggests a primary epidermal

TABLE 44-1

Drugs That Cause Exfoliative Dermatitis

Allopurinol*	Lithium
Aminoglycosides	Mefloquine
Aminophylline	Mercurials
Amiodarone	Mesna
Amonafide	Methylprednisolone
Ampicillin	Minocycline
Antimalarials	Mitomycin C
Arsenicals	Omeprazole
Aspirin	Penicillin
Aztreonam	Pentostatin
Bactrim	Peritrate and glyceryl trinitrate
Barbiturates	Pheneturide
Bromodeoxyuridine	Phenolphthalein
Budesonide	Phenothiazines
Calcium channel blockers	Phenylbutazone
Captopril	Phenytoin
Carbamazepine	Phototherapy
Carboplatin	Plaquenil
Cefoxitin	Practolol
Cephalosporins	Quinidine
Cimetidine	Ranitidine
Cisplatin	Retinoids
Clofazamine	Ribostamycin
Clofazamine	Rifampin
Codeine	St John's wort
Cyanamide	Streptomycin
Dapsone	Sulfasalazine
Dideoxyinosine	Sulfonamide antibiotics
Dilunilal	Sulfonylureas
Diphenylhydantoin	Tar preparations
Ephedrine	Terbinafine
Ethambutol	Terbutaline
Ethylendiamine	Thalidomide
Etretinate	Thiacetazone
Fluorouracil	Thiazide diuretics
GM-CSF	Ticlopidine
Gold	Timolol maleate eyedrops
Herbal medications	Tobramycin
Indeloxazine hydrochloride	Tocainide
Indinavir	Trimetrexate
Interleukin-2	Trovafoxacin
Iodine	Tumor necrosis factor- α
Isoniazid	Vancomycin
Isoorbide dinitrate	Yohimbine
Lansoprazole	Zidovudine
Lidocaine	

*The more commonly implicated agents are listed in bold.

etiology. It is likely that exfoliative dermatitis represents an end-stage inflammatory state that affects the entire integument, in which there is an uncontrolled feedback loop between the epidermis and the dermis.

The epidermis produces significantly elevated amounts of circulating vascular permeability factor/vascular endothelial growth factor in erythrodermic skin, resulting in dermal vascular proliferation and increased vascular permeability.¹³ The increases in adhesion molecule expression (VCAM-1, ICAM-1, E-selectin, and P-selectin) seen in exfoliative dermatitis promote chronic dermal inflammation, which may, in turn, promote both epidermal proliferation and epidermal production of inflammatory mediators.¹⁴ The dermal infiltrates may demonstrate either a T_H1 cytokine profile, as in benign reactive exfoliative dermatitis, or a T_H2 cytokine profile, as in Sézary syndrome.¹⁵ This finding is consistent with the fact that a wide range of distinct immunologic processes (e.g., atopic dermatitis and contact dermatitis) may produce exfoliative dermatitis. Alterations in levels of various pro-inflammatory

molecules (interleukins 2, 3, and 8; interferon- γ ; and ICAM-1) also have occurred with exfoliative dermatitis. However, these changes may be a secondary factor in the exfoliative dermatitis rather than an immunopathogenic cause.

The basic pathophysiology of exfoliative dermatitis involves an increased rate of epidermal turnover. The number of germinative cells and their absolute mitotic rate increase, whereas the transit time of keratinocytes through the epidermis decreases. Consequently, more cellular material is lost from the surface. Because of the rapid cell turnover in exfoliative dermatitis, the stratum corneum retains a number of components that are normally resorbed or metabolized. The desquamated cells show increased amounts of nucleic acids and their degradation products, as well as increased amounts of soluble protein. Although the large amount of protein lost each day has a potentially adverse effect on systemic metabolism (see below), the losses of nucleic acids and other minor constituents are too small to be of metabolic significance.

CLINICAL MANIFESTATIONS

Dermatologic Manifestations

Despite the wide range of underlying dermatologic disorders that may lead to exfoliative dermatitis, the clinical manifestations in all cases are similar. The disease generally starts as erythematous patches resulting from capillary dilation. Over days to weeks, these patches spread until bright red erythema affects the entire skin surface. The epidermis appears thin, giving the skin a shiny appearance.

Desquamation begins a few days after the onset of the erythema and often appears first in flexures. The scales are generally white or yellow and fine, although large platelike sheets of scale may develop, particularly in acute stages and on the palms and soles. As the desquamation progresses, the skin appears dry with a dull scarlet color and a gray hue. It is covered with small laminated scales that exfoliate profusely (Fig. 44-1). In some cases, particularly in the presence of bacterial colonization, there may be profuse moist, adherent crusts, leading to a characteristic musty odor.¹¹ A purple hue is often evident in dependent areas, and there may be straw-colored exudates.

With time, induration and thickening of the skin from a combination of edema and lichenification may impart a sensation of severe skin tightness to the patient. In mild or early exfoliative dermatitis, the disease may be apparent only by blanching of the skin to demonstrate the mild macular erythema. In darkly pigmented patients, this early sign may be easily overlooked.

Chronic exfoliative dermatitis results in diffuse shedding of hair. The nails become thickened, ridged, dull, and brittle. Subungual hyperkeratosis, distal onycholysis, and splinter hemorrhages are common, and occasionally, the nails may be shed. Paronychia, onycholysis, subungual hyperkeratosis, and Beau lines of the nails may develop.¹ Once these changes develop, they generally overshadow any nail findings of the underlying disease process. "Shoreline" nails, reported to be a specific manifestation of drug-induced exfoliative dermatitis, are characterized by alternating bands of nail plate discontinuity and leukonychia representing periods in which the offending drug was used.¹⁶ Chronic periorbital involvement, resulting in induration and decreased laxity of the eyelids, may lead to ectropion and epiphora. Palmoplantar keratoderma with thick, fissured scales has been reported in up to 80 percent of patients with chronic exfoliative dermatitis, and crusted, seborrheic scaling of the scalp is common.¹⁷ Exfoliative dermatitis does not generally involve mucosal surfaces.