

## Managing comorbid disease in patients with psoriasis

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Psoriasis is a common, chronic inflammatory skin disease that typically presents with sharply demarcated, red scaly dermatological plaques that may be painful and stigmatising (fig 1). It causes a high burden of disease, comparable to that of cancer or diabetes mellitus.<sup>1</sup> In about a quarter of people with psoriasis the condition is severe enough for them to need ultraviolet light therapy, systemic drug treatment, or hospital admission.

Three recent developments have changed our understanding of psoriasis substantially. Firstly, researchers identified “Th17 cells” (a new type of lymphocyte) as important effector cells in autoimmune diseases.<sup>2</sup> Indeed, the first drug that interferes with the functions of Th17 cells was approved in 2009, its first indication being psoriasis.<sup>3</sup> Secondly, psoriasis is now confirmed as a systemic disease, as serum biomarkers for inflammation are raised in patients with psoriasis.<sup>4</sup> Finally, psoriasis frequently occurs alongside other diseases.<sup>5</sup> This review focuses on comorbid diseases and their relation to psoriasis, and we highlight how the presence of comorbidities influences treatment decisions and management for patients with psoriasis.

### Which comorbidities are now recognised as important in psoriasis?

The notion of psoriasis being just a skin disease has been challenged by several large epidemiological studies, in which between 7% and 40% of patients with psoriasis eventually developed psoriatic arthritis.<sup>6</sup> The course of psoriatic arthritis is comparable to that of rheumatoid arthritis, as about half of patients show a progressive disease, eventually exhibiting erosions and loss of function in affected joints.<sup>6</sup> Conventional disease modifying antirheumatic drugs, such as methotrex-



**Fig 1** | Patient with severe psoriasis: red scaly plaques cover more than 10% of the body surface area; this patient also has a body mass index >25

ate, have not been shown to prevent progressive joint destruction, whereas tumour necrosis factor  $\alpha$  blocking agents seem to have this potential, and they are recommended as second line therapeutics in psoriatic arthritis.<sup>7</sup>

A landmark study based on a cohort of almost 3000 patients found an association between psoriasis and

### SUMMARY POINTS

Psoriasis is a common and severe disease, impairing patients' quality of life to an extent similar to other major diseases such as cancer or diabetes mellitus  
Psoriasis is a systemic disease: Th17 cells are important effector cells and biomarkers of systemic inflammation are raised

Several important diseases including psoriatic arthritis, metabolic syndrome, Crohn's disease, cancer, and depression are associated with psoriasis

Life expectancy is reduced by about four years in patients with severe psoriasis, primarily owing to their increased cardiovascular risk

Physicians in primary and secondary care need to detect developing comorbidities early, using validated questionnaires (to detect psoriatic arthritis) and proper monitoring

Treatment decisions must take into account patients' comorbidities (to identify contraindications) and comedication (to avoid drug interactions)

### SOURCES AND SELECTION CRITERIA

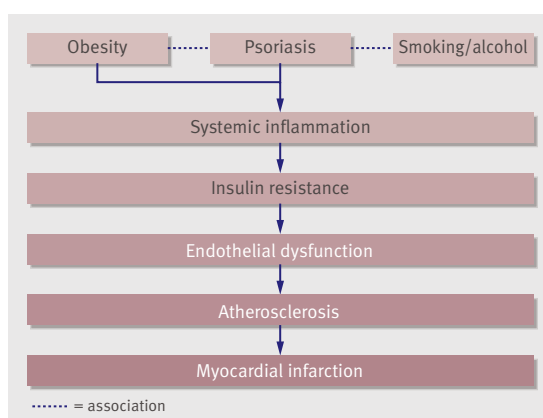
We initially discussed the topic of this review with experts from outside dermatology, including internists from different specialties and scientists in the field of cardiovascular research. Subsequently, we searched Embase and Medline for systematic reviews, randomised trials, large population based studies, and case-control studies published between 1995 and 2009. We used the search terms “psoriasis”, “risk factors”, “obesity”, “diabetes mellitus”, “hypertension”, and “smoking”. Additional information cited includes evidence-based guidelines and published consensus statements.

### A PATIENT'S PERSPECTIVE

I was a trained surgeon and ambitious tennis player when I encountered my first psoriatic rash at the age of 30; my joints became affected a few years later. Unable to trust my hands any longer, I quit my job and chose an office rather than a theatre as my future working environment. It is impossible to tell if it was the stigmatising skin symptoms or the less than rewarding office work that gradually changed my optimistic personality and active lifestyle.

Over the years, many doctors tried to help me control the disease, without much success. When I realised that sunlight and a relaxed pace did me good, I tried to spend as much time as possible in the Mediterranean region, eventually buying a house there. It was not until the age of 60 that I had the opportunity to use a tumour necrosis factor  $\alpha$  blocking biologic and felt I was in full control of my body again. In fact, I felt so great that I decided to make a dream come true: I travelled to Nepal and hiked to Mount Everest Base Camp. However, despite all this and also being slim, I had a heart attack one year later. It makes me feel uneasy to understand that psoriasis goes way beyond skin and joints.

**Fig 2 | The “psoriatic march,”** whereby psoriasis and its comorbidities, including obesity, contribute to the inflammatory burden of affected patients, resulting ultimately in myocardial infarction if coronary arteries are involved



diabetes mellitus, obesity, heart failure, and hypertension<sup>8</sup>—findings that have since been reproduced and extended in several other studies. The metabolic syndrome—which comprises abdominal obesity, arterial hypertension, abnormal oral glucose tolerance, and abnormal blood lipids—is the most important comorbidity of psoriasis.<sup>5</sup> Patients with psoriasis have a fivefold increase in risk of developing type 2 diabetes, and double the risk of a myocardial infarction. A large, population based study found that life expectancy was about four years shorter in patients with severe psoriasis than in healthy controls.<sup>9</sup> Other important comorbidities include Crohn's disease, depression, and cancer.<sup>15</sup>

Lifestyle risk factors for heart disease have been observed in patients with psoriasis more often than in controls. Evidence derived from population based observations and from case-control studies shows that patients with psoriasis are more likely to be active smokers<sup>10</sup> and consume more alcohol.<sup>11</sup>

### How is psoriasis related to its comorbidities?

Researchers have found associations between comorbidities and psoriasis on the basis of epidemiological data. Genetic, immunological, and clinical studies have strengthened these associations and suggest genetic links between psoriasis and some of its comorbidities.

Genome-wide association studies have identified variations in the genes encoding the interleukin-23 receptor and a region of interleukin-12B as indicators of an increased risk of developing psoriasis; interleukin-23 receptor has also been associated with an increased risk of psoriatic arthritis.<sup>12</sup> Another gene, CDKAL1 (CDK5 regulatory subunit associated protein

1-like 1), is associated with psoriasis as well as with Crohn's disease and type 2 diabetes mellitus.<sup>13</sup>

As both psoriasis and myocardial infarction have been associated with the metabolic syndrome, an indirect link between the two may exist, although the concept of psoriasis itself being a cardiovascular risk factor has only recently been proposed. Two large population based studies recently established a “dose-response curve” between the severity of psoriasis and cardiovascular mortality.<sup>14 15</sup> Depending on age and disease severity, patients with psoriasis may have as much as a threefold increased risk of myocardial infarction,<sup>15</sup> and calcification of the coronary arteries is more frequent and pronounced in patients with psoriasis than in controls matched for other known risk factors.<sup>16</sup> As coronary artery calcification reflects coronary artery disease, these findings strengthen the idea that psoriasis is indeed an independent risk factor for cardiovascular disease.

Pathophysiologically, the increased cardiovascular mortality of patients with psoriasis seems to be a consequence of what we have termed the “psoriatic march”: psoriasis and its comorbidities, including obesity as part of the metabolic syndrome, all contribute to a patient's systemic inflammatory burden (fig 2).<sup>17</sup> Systemic inflammation in turn causes insulin resistance, a state in which the equilibrium between proatherogenic and antiatherogenic effects of insulin is shifted towards proatherogenic effects.<sup>18</sup> This shift expedites endothelial dysfunction, which then leads to atherosclerosis and eventually myocardial infarction if coronary arteries are involved. In line with this concept, several cross sectional studies have independently described a correlation between psoriasis severity and the patients' blood levels of adipokines, soluble mediators interfering with insulin functions. Overall, the mechanisms outlined here suggest a metabolic state comparable to that in patients developing type 2 diabetes mellitus.<sup>19 20</sup>

### How can comorbidities be diagnosed early?

Two recent large surveys of German physicians found that psoriatic arthritis as a classic comorbidity is underdiagnosed and that other comorbidities are not regularly assessed.<sup>21 22</sup>

### Psoriatic arthritis

Psoriatic arthritis is often chronic and progressive. Early diagnosis and treatment can prevent joint destruction and loss of function.<sup>23</sup> As psoriasis of the skin precedes joint involvement by about a decade in most cases, general practitioners or other non-rheumatologists may be the ones to identify arthritic changes early. Three large validation studies recently identified three patient questionnaires as being highly sensitive and specific tools to diagnose psoriatic arthritis.<sup>19</sup> These questionnaires are the Toronto psoriasis arthritis screen (ToPAS)<sup>24</sup> the psoriatic arthritis screening and evaluation (PASE) tool,<sup>25</sup> and the psoriasis epidemiology screening tool (PEST).<sup>26</sup> The ToPAS questionnaire has been developed to screen for psoriatic arthritis in unselected patients, and the PASE and PEST questionnaires are intended to identify psoriatic arthritis among patients with psoriasis.

### Other comorbidities

An initiative of the US patients organisation the National Psoriasis Foundation recently resulted in a checklist for the management of patients with psoriasis with a list of simple,

## ONGOING RESEARCH

- To understand the pathogenic link between psoriasis and its comorbidities
- To clarify the relation between psoriasis and psoriatic arthritis
- To assess the impact of the treatments for comorbidities on psoriasis
- To assess the effects of lifestyle intervention on the efficacy of pharmacotherapy

## Unanswered questions

- How does long term systemic treatment for psoriasis affect cardiovascular risk? What are the differences between the currently available treatment modalities?
- Would early aggressive treatment of psoriasis prevent the onset of psoriatic arthritis?
- Will treatments targeted at Th17 cells have effects beyond the skin?
- What outcome should we aim for when treating psoriasis and its comorbidities?

## TIPS FOR NON-SPECIALISTS

- Only severe psoriasis confers a substantially increased cardiovascular risk. Psoriasis should be considered to be severe if it affects more than 10% of the body surface area or if the patient has ever been treated on an inpatient basis or has needed ultraviolet light therapy or systemic drug treatment
- Every patient with psoriasis should be screened for psoriatic arthritis, using a validated questionnaire (such as ToPAS,<sup>24</sup> PASE,<sup>25</sup> or PEST<sup>26</sup>)
- Look for other developing comorbidities by measuring heart rate, blood pressure, body mass index, fasting blood lipids, and fasting glucose
- If comorbidities are present, treat according to the respective guidelines or refer to a specialist
- If a systemic treatment for psoriasis is indicated, consider potential contraindications and drug interactions as consequences of comorbidities and comedication
- If a patient is obese or smoking, try to support him or her to adopt a healthier lifestyle, normalise body weight, and quit smoking

useful investigations that may be performed by physicians in primary and secondary care (see table on [bmj.com](#)).<sup>27</sup> As with psoriatic arthritis, early diagnosis will allow timely management of developing comorbidities.

**How might comorbidities influence treatment decisions?**

Guidelines recommend a wide spectrum of systemic drugs to treat severe psoriasis.<sup>28</sup> Several systemic drugs for psoriasis may increase a patient's risk of developing cardiovascular disease. The retinoid acitretin may increase serum triglycerides and cholesterol, and ciclosporin may carry the risk of difficult to control hypertension. Recent European guidelines on systemic treatment of psoriasis recommend regular monitoring of serum parameters (including lipids) as well as blood pressure to detect these potential adverse effects of psoriasis treatment.<sup>28</sup>

However, treating comorbidities, which often require multiple medications, may worsen psoriasis. In a large, multicentre survey of 1200 patients treated for psoriasis as inpatients, three quarters were taking medication for comorbidities, with a quarter taking more than three systemic drugs.<sup>29</sup> Several of these concomitant medications, such as  $\beta$  blockers or angiotensin converting enzyme inhibitors, are either known or strongly suspected to trigger or worsen psoriasis. In the survey 8% of the patients were taking a  $\beta$  blocker and 12% an angiotensin converting enzyme inhibitor.

Drug interactions are another potential problem of comedication. For example, the concentration of ciclosporin may increase if it has to compete with other drugs for enzyme substrates in the process of hepatic metabolism via the cytochrome P450 system.<sup>30</sup> This may result in a higher likelihood of side effects.

**What's new in psoriasis management?**

The management of psoriasis has shifted away from solely

treating a skin disease towards comprehensive disease management. This new approach calls for an active role for general practitioners and dermatologists and a coordinated input from rheumatologists and diabetologists.

Experts are now aware that patients with psoriasis are at risk of developing additional health problems, and they agree that blood pressure, heart rate, body mass index, fasting blood lipids, and fasting blood glucose should be measured regularly in these patients.<sup>27</sup> They also strongly recommend using screening questionnaires such as ToPAS,<sup>24</sup> PASE,<sup>25</sup> or PEST<sup>26</sup> to identify psoriatic arthritis.

As psoriasis can be controlled but not cured, and as it seems to be a risk factor for cardiovascular disease, patients must be advised to eliminate avoidable additional risk factors for cardiovascular diseases, such as obesity and smoking. Ideally, this would be part of a comprehensive lifestyle intervention, similar to that established in the management of diabetes mellitus.

National and international treatment guidelines for psoriasis recommend that drugs that potentially worsen cardiovascular risk factors—such as through raising blood lipids or increasing blood pressure—should be avoided in patients at risk.<sup>28</sup> Similarly, in patients with several concomitant diseases, avoidance of drug interactions may be an important goal (though one that is sometimes difficult to achieve) when choosing the best treatment option for an individual. For patients with many comorbidities, the biologics approved for the treatment of psoriasis—namely, adalimumab, etanercept, infliximab, and ustekinumab—are valuable therapeutic options. According to their label, these drugs may be used in patients for whom conventional systemic psoriasis drugs are contraindicated (including patients with hypertension or dyslipidaemia).<sup>31</sup>

**What can we learn from psoriasis as a model of an immune mediated inflammatory disorder?**

Psoriasis has evolved into a model for what are classified as immune mediated inflammatory disorders. These are chronic inflammatory diseases that include rheumatoid arthritis, Crohn's disease, and multiple sclerosis, all of which share a central pathogenic role of a disordered immune system. Thus, insights into the pathogenesis of psoriasis may help to develop new treatments, which may also be effective in other immune mediated inflammatory disorders. A recent example is the discovery of an antibody interfering with Th17 cells, which was recently approved for the treatment of psoriasis but also showed good efficacy for the treatment of psoriatic arthritis in a large randomised controlled trial.<sup>32</sup> This antibody may well prove effective in treating other immune mediated inflammatory disorders. Monomethyl fumaric acid ester, the active compound in a mixture of fumaric acid esters currently approved for the treatment of psoriasis in Germany, is now being developed by a major pharmaceutical company for use in treatment of multiple sclerosis; it may be useful for other immune mediated conditions too.

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**Patient consent obtained.**



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## ANSWERS TO ENDGAMES, p 219. For long answers go to the Education channel on bmj.com

### PICTURE QUIZ A 56 year old man with headache, fever, and neurological symptoms



- 1 Acute infective meningoencephalitis, intracranial venous sinus thrombosis, cerebral abscess, and subdural empyema must all be considered given the fever and focal neurological signs. Autoimmune disorders such as Bickerstaff's brainstem encephalitis and neurosarcoidosis are also possible but are less likely given the patient's high temperature.
- 2 The T2 weighted magnetic resonance imaging scan shows right sided cerebellar hyperintensities and a left sided pontine T2 hyperintensity, in keeping with acute inflammation or infarction (figure).
- 3 The most likely diagnosis is meningitis with rhombencephalitis secondary to infection with *L monocytogenes*. This can often be confirmed on Gram stain and culture of cerebrospinal fluid—the presence of Gram positive rods in the cerebrospinal fluid is highly specific for *Listeria*. If culture is negative then 16S polymerase chain reaction (PCR), a broad range test for bacterial ribosomal DNA, can be used to screen for a range of bacterial infections. Blood cultures should be taken because they can be useful if positive.
- 4 Our patient should be treated empirically with broad spectrum cephalosporins according to local policy together with ampicillin (or amoxicillin) at a dose of 2 g every four hours for 21 days to cover the possibility of *Listeria* meningoencephalitis.

T2 weighted magnetic resonance imaging scan of the brain showing high signal in keeping with infarction in the pons (upper arrow) and right cerebellum (lower arrow)

### STATISTICAL QUESTION

#### Placebos

Answers a, b, c, and d are all true.

### CASE REPORT A woman with hypophosphataemia and raised alkaline phosphatase

- 1 The patient has primary hyperparathyroidism; vitamin D replacement seemed to unmask the hypercalcaemia.
- 2 Further investigations include:
  - Twenty four hour urine for calcium to exclude familial hypocalciuric hypercalcaemia.
  - Dual energy x ray absorptiometry to assess bone mineral density.
  - Preoperative parathyroid scintigraphy (sestamibi labelled with technetium-99m) or ultrasound (or both) if minimally invasive parathyroidectomy is being considered.
- 3 Parathyroidectomy is the only appropriate treatment provided surgical criteria are fulfilled.