

Mycosis Fungoides

What is mycosis fungoides?

Mycosis fungoides is a T-cell lymphoma of the skin. The disease is caused by the proliferation of T-lymphocytes, also known as helper T cells. The cells bear the T-cell antigen CD4+ and frequently lack other normal T-cell antigens, such as CD7. In 1806, the term mycosis fungoides was first used by Jean-Louis Marc Alibert, a French dermatologist, when he described a severe disorder in which tumours resembling mushrooms presented on a patient's skin. The term cutaneous T-cell lymphoma (CTCL) was coined in 1979 to describe a heterogeneous group of malignant T-cell lymphomas with primary manifestation in the skin.

Mycosis fungoides is the most common type of CTCL, and represents some two per cent of all lymphomas. It is a highly symptomatic disfiguring disease, which is life threatening in the advanced stages, and there are no spontaneous remissions. Its causes remain unknown. Various theories implicate occupational or environmental exposures, other forms of chronic antigenic stimulation, or viral exposures. Patients usually survive for many years after diagnosis, but mycosis fungoides is largely incurable, excepts in a subset of very early stage patients who may sustain durable remissions.

Who does mycosis fungoides affect?

The incidence in Europe is approximately 1,200 new cases a year, with a prevalence of about 16,000 patients. In the USA, the incidence is ca. 0.4 per 100,000 population, and there are about 1,000 new cases per year. The prevalence of the disease is estimated to be 16,000 to 20,000. Mycosis fungoides manifests in the skin as a progressive disease, more common in men (the male to female ratio is 2:1), with an age range of usually between 45 and 65 years. The disease may progress from eczema-like skin lesions to ulcerative tumours. Duration from the onset of skin symptoms to diagnosis is about six years.



Early in the course of disease, skin lesions may be non-specific, so confusion with benign conditions is common. Over time, mycosis fungoides becomes more aggressive, and in about 20 per cent of patients the disease will undergo a transformation to highly malignant lymphoma with widespread dissemination into various organs of the body. Late-stage disease is associated with the decline of the immune system. Death often results from systemic infection, especially with *Staphylococcus aureus* or *Pseudomonas aeruginosa*, and other organisms.

Stages in mycosis fungoides

Stage I

- The cancer only affects parts of the skin, which has red, dry, scaly patches, but no tumours. The lymph nodes are not larger than normal.

Stage II

Either of the following may be true:

- The skin has red, dry, scaly patches, but no tumours. Lymph nodes are larger than normal, but do not contain cancer cells;
- There are tumours on the skin. The lymph nodes are either normal or are larger than normal, but do not contain cancer cells.

Stage III

- Nearly all of the skin is red, dry, and scaly. The lymph nodes are either normal or are larger than normal, but do not contain cancer cells.

Stage IV

The skin is involved, in addition to either of the following:

- Cancer cells are found in the lymph nodes;
- Cancer has spread to other organs, such as the liver or lung.

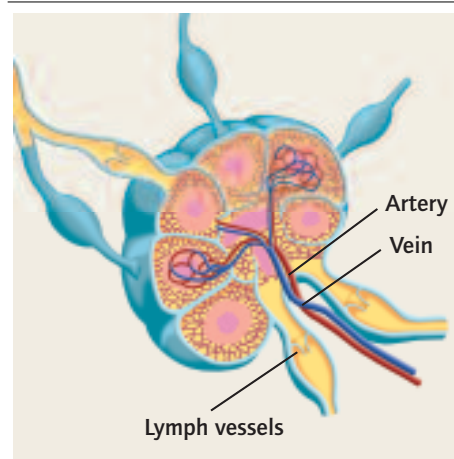
Mycosis fungoides is a cancer of the skin. It is highly disfiguring and life threatening. Treatments will be adapted to the severity of the disease. However, a cure remains a challenging goal for the pharmaceutical industry.

Present treatments

Relief of symptoms and improvement in cosmetics are the goals of treatment, as it is generally agreed that mycosis fungoides is not curable with the therapies currently available. Standard and experimental treatments include local therapy with various substances, phototherapy, photopheresis, radiotherapy, various systemic chemotherapeutic agents, biological response modifiers such as interferon-alpha (IFN-alpha), retinoids, various monoclonal antibodies and bone marrow transplantation. All current therapies are associated with a number of unpleasant side effects, including the possibility of inducing other cancers. Some treatments have an inadequate efficacy, are time-consuming, and/or cannot be repeated more than a few times.

Therapy of mycosis fungoides is stage-related. In early stage plaque disease (I and IIA), topical nitrogen mustard – as daily application to almost all skin surfaces for six to twelve months – is considered first line therapy, with reported response rates ranging from 30 to 60 per cent, including up to 20 per cent long-term complete responses. Responses are observed more commonly in patients with few plaques as compared to those with generalised plaque involvement. Topical therapy with corticosteroids to inhibit intercellular adhesion and T-lymphocyte binding to the inner lining of blood vessels is also a common approach. Topical treatment with a retinoid gel is also an option for the treatment of early stage disease.

Photo chemotherapy – a combination of psoralen which is activated by ultraviolet A light (PUVA) – is a commonly used therapy for stage IIA. For patients with advanced forms, i.e. for stage IIB disease, electron beam therapy is an effective initial therapy resulting in long-term remissions in some cases. The treatment is technically demanding and availability thus limited to specific centres. Furthermore, radiation regimes can only be given a few times, due to late radiation effects on the skin. Extracorporeal photo chemotherapy (photopheresis) includes the removal of an amount of the patient's blood by plasmapheresis, the treatment of the separated



Lymph node and lymph vessels



Mycosis fungoides

Courtesy of Prof. E.G. Jung, Heidelberg, Germany
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leukocytes with PUVA, and the re-infusion of treated blood. The approach is believed to reverse the imbalance of T-cells, to increase turnover of T-lymphocytes and is commonly used for stage III or erythrodermic disease. Clinical studies have demonstrated complete response rates of more than 50 per cent.

Compounds reported to show clinical activity in mycosis fungoides of stage IV and refractory forms of the disease include chemotherapeutic agents. Also, combination chemotherapy regimens such as CVP and CHOP are applied. Drawbacks of combination chemotherapy are infectious complications. Short response duration often outweighs the modest response rates. Skin-directed therapy with chemotherapeutic agents is used palliatively in patients with advanced mycosis fungoides and induces significant, but relatively short-lived, responses.

Retinoids are vitamin A analogues involved in modulation of cell growth. Their biologic effects result from alterations in gene expressions that are mediated through two major types of nuclear receptors, the retinoic acid receptor (RAR) and the retinoic X receptor (RXR). Recently, an orally applied RAR agonist has been approved in the EU as systemic treatment in patients with refractory mycosis fungoides. RAR agonists are considered to block proliferation and promote differentiation of T-lymphocytes. Another new approach is the use of a fusion toxin protein. The compound consists of diphtheria toxin conjugated to interleukin-2 (IL-2). The toxin is released inside malignant cells expressing the IL-2 receptor.

What's in the development pipeline?

Clinical research groups are studying the effects of Biological Response Modifiers. Interferons are believed to have antiproliferative, cytotoxic and immunomodulating effects. IFN-alpha has been shown to lead to response rates of up to 90 per cent in minimally pretreated patients, while response rates in more heavily treated or refractory groups of patients were closer to 50 per cent. Interleukins (ILs), such as IL-2 and IL-12 are also subject of investigations. IL-2 is deficient in malignant mycosis fungoides cells. IL-12 is essential for anti-tumor cytotoxic T-cell response and involved in interferon-gamma (IFN-gamma) production.

Other researchers are studying the clinical effect of infusions of human monoclonal antibodies (huMabs) which are directed against T-cell targets. In May 2004, the EU granted orphan drug status to a huMab against the target CD4+ for cutaneous T-cell lymphoma. Other multi-centre clinical trials to study the efficacy of this huMab directed against CD4+ are underway.

An inhibitor of the activity of histone deacetylase is being studied in clinical trial phase 2. The study includes patients with advanced CTCL. A phase 1/2 trial studies an immunostimulatory oligodeoxynucleotide for the treatment of patients with stage IB to IVA mycosis fungoides. Another phase 1 trial is testing the efficacy of an oral purine nucleoside phosphorylase (PNP) inhibitor. A phase 2 trial with a novel murine monoclonal antibody is underway to treat patients with CD30+ malignancies. The antibody is reported to have specificity for the T-cell target CD30 that is unique from other anti-CD30 antibodies.

The longer-term future

Treatment of mycosis fungoides is still an unmet medical need. Future research will study which nuclear receptor molecules are activated to alter the function of T-lymphocytes, changing them into malignant T-cells. Investigations will also focus on molecules which modulate the activity of such cells and may work improperly. Findings in this area would be a promising step in developing a specific therapy for people with this chronic and devastating disease.

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