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Viral infection, atopy and mycosis fungoides: A European multicentre case–control study

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Abstract

Mycosis fungoides (MF) is a rare disease with an unknown aetiology, although it has been suggested that infections may play a role. The present study investigates whether infections, atopic disorders and some other diseases are risk indicators for MF. A European multicentre case–control study involving seven rare cancers, including MF, was conducted from 1995 to 1998. Patients between 35 and 69 years of age diagnosed with MF ($n = 140$) were recruited, and the diagnoses were verified by a reference pathologist, who classified 83 cases as definitive and 35 cases as possible; 22 cases were not accepted. Of the 118 accepted cases, 104 patients were interviewed (including 76 definitive cases and 28 possible cases). These 76 definitive cases were used for this study. A common set of controls to serve all case groups were interviewed, representing a total of 4574 controls. The latter included 1008 colon cancer patients and 3566 subjects selected from population registers. Information on infections, skin pathology and clinical history 5 years before the diagnosis of MF was used to estimate odds ratios (ORs) derived from logistic regression-modelling, which included gender, age and country. The highest ORs for MF were found in patients who reported a history of psoriasis 5 years before MF was diagnosed (OR 7.2, 95% CI: 3.6–14.5). Urticaria had an OR of 1.4 (95% CI: 0.6–3.6). Infections and atopic diseases were not closely associated with MF. Some diseases correlate to MF. Whether this has a causal background or reflects early diagnostic uncertainty is not known.

Keywords: (MEDLINE): Mycosis fungoides; Infectious diseases; Clinicopathological factors; Case–control study

1. Introduction

Cutaneous T-cell lymphoma (CTCL) is a lymphoproliferative disorder involving neoplastic T cells. Lymphomas have a wide range of clinical manifestations, including mycosis fungoides (MF) [1]. The incidence of MF has been increasing [2–4]. The annual incidence of non-Hodgkin's lymphomas is increasing by 3–4% in different parts of the developed world [5].

Chronic dermatitis has been associated with an increased risk of MF [6]. Greene and colleagues [7] studied antecedents of allergy, fungal and viral skin

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infections among MF cases, but the study did not include a control group. Individuals infected with human T-cell leukaemia virus type I (HTLV-I) may develop T-cell leukaemia with skin involvement indistinguishable from those of CTCL. These observations have led some authors to hypothesise that CTCL may be a consequence of infection with HTLV-1 or some other unknown retrovirus (L.D. Wilson, SEER Program, National Cancer Institute, Bethesda, MD, USA, 1995).

Diagnosing early stages of MF is often difficult [8,9]. Patients with early MF have long-standing erythematous patches or thin plaques that clinically appear more like inflammatory dermatosis than a neoplastic process. MF is a disease with a slow, indolent course. Lever and Shaumburg-Lever [10] accepted that small plaques (parapsoriasis) or digitate dermatosis are benign disorders unrelated to MF, but Hu [11] concluded that approximately 10–30% of cases with parapsoriasis progressed towards MF. Early stage MF closely resembles chronic dermatitis, both clinically and histologically.

In this study, we investigated the associations between MF and a number of non-malignant diseases.

2. Patients and methods

As part of a European multicenter case–control study, we enrolled cases and controls aged between 35 and 69 years from 1995 to 1998. The study was designed to evaluate occupational and other risk factors of seven rare cancers of: the small bowel, thymus, bone, eye (melanoma), gallbladder, male breast and MF, using a common control group. The 140 MF cases were recruited from Denmark, Sweden (Umea, Örebro/Uppsala, Linköping, Lund), France (Calvados, Côte d'Or, Doubs, Hérault, Isère, Manche, Bas-Rhin, Haut-Rhin, Somme, Tarn), Germany (Hamburg/Bremen, Essen/Saarland), Italy (Torino, Firenze, Padova), and Spain (Valencia, Navarre and the Basque Country).

Incident cases of MF were identified according to ICD codes and codes from the International Classification of Diseases for Oncology (ICD-O 1976: Morphology and Topocode). Cases were selected if they had topography codes 173.0–173.9 with morphology codes 97003–970013. Case ascertainment (with clinical and pathological diagnosis of MF) was based upon repeated requests to hospital departments, pathology departments and/or by frequent screening of regional or national cancer and pathology registers. For all centres, the study base was defined by geographical borders, except in Spain, where the catchment area of the participating hospital of the MF cases defined the study base.

All diagnoses were checked by the reference pathologists who identified the following characteristics: (1) multiple Pautrier microaggregates; (2) diffuse infiltration of many individual atypical lymphocytes; (3) a few small intraepidermal clusters of atypical lymphocytes; (4) a few individual intraepidermal atypical lymphocytes; (5) a dense upper dermal, bandlike interface infiltrate including atypical lymphocytes; (6) a mild to moderate pleomorphic upper dermal infiltrate with atypical lymphocytes focally exhibiting an interface pattern; and (7) extension of the infiltrate into the deep dermis. A definitive diagnosis of MF was made if criteria 1 or 2 or $3+4+5$ or $3+4$ plus $6+7$ were present. The review was based on one routinely stained biopsy, in each case involving precise previously described criteria. Cases not fulfilling the criteria, but exhibiting some features of MF were classified as possible cases. The reference pathologist accepted 84% (118 cases) of the 140 patients ascertained by a pathologist who reviewed a representative histological slide from all cases together with the report from the local pathology department, without access to the exposure status. In this paper, we present the results based upon interviews of 76 of the 83 subjects classified as definitive cases (76 cases), and of 28 of the 35 that were classified as possible (28 cases) by the reference pathologist.

Population controls were randomly selected from the regions of case ascertainment. They were frequency-matched with the combined set of cases from all seven cancer sites included in the study, in order to obtain at least four controls in each stratum defined by: age (5-year interval), gender and region. Population registries or electoral rolls were used for sampling controls in Denmark, Sweden, France, Germany and Italy. Since no population registry was available in Spain, patient controls with colon cancer were selected from the hospitals that provided the cases by a procedure identical to that used for the cases.

Altogether 1008 colon cancer controls (580 from Spain and 428 from Denmark) and 3566 population controls were enrolled (in total: 4574 controls).

Table 1 provides data concerning the recruitment and the pathology review for MF by country.

A set of common questionnaires on occupational exposures, diseases and lifestyle factors was used. The questionnaires were developed and tested in cooperation with all of the participating centres. The original version was written in English and translated into Danish, Swedish, German, French, Italian and Spanish. Back-translation to English was performed to ensure non-ambiguity in the phrasing of the questions.

2.1. Exposure assessment

Questions on symptoms, diseases and illnesses related to any organ or system that the person had had 5 years before the diagnosis of MF for cases, or 5 years before the interview for controls, were included in the questionnaire. The questions had the fixed answering categories: yes,

Table 1
Select characteristics of cases with MF and controls

Country	Cases					Controls		
	Identified N	Pathology review		Interview		Eligible N	Interview	
		Definitive	Possible	Yes	No		Yes	No
Denmark	11	7	4	6 (55%)	5 (45%)	1011	574 (57%)	437 (43%)
Sweden	3	3		3 (100%)		407	230 (57%)	177 (43%)
France	28	19	9	26 (93%)	2 (7%)	630	485 (77%)	145 (23%)
Germany	8	4	4	6 (75%)	2 (25%)	1541	732 (48%)	809 (52%)
Italy	23	13	10	20 (87%)	3 (13%)	405	304 (75%)	101 (25%)
Spain	45	37	8	43 (96%)	2 (4%)	580	579 (100%)	1 (<1%)
Total	118	83	35	104 (88%)	14 (12%)	4574	2904 (64%)	1670 (36%)

MF, mycosis fungoides.

no, don't know. Questions related to infections and skin diseases as potential risk indicators. Association with other diseases, for which we have no *a priori* hypothesis are also reported (Table 2).

2.2. Analyses

We calculated crude odds ratios (OR) and ORs adjusted by age, gender and country for specific diseases present 5 years prior to the interview. Adjusted ORs were obtained by using unconditional logistic regressions which included the frequency matching variables gender, age and country in the model. Two-sided 95% confidence intervals (CI) are given. Further details about the study have been provided elsewhere in Ref. [12].

Information on potential confounders to be included in the analysis was based upon a review of the literature and discussions among the authors in the planning phase. Variables that changed the effect measure more than 10% (the OR for the exposure under study) when dropped one by one from the full logistic model, were considered to confound and were therefore included in the model.

Table 2
Odds ratios (ORs) for definitive cases of MF according to infections or atopic dermatitis reported 5 years before MF was diagnosed

	Definitive cases of MF	Controls	Definitive cases		
			ORc	ORa	C.I. 95%
Mumps or herpes or hepatitis					
No	32	1184	1	1	Reference
Yes	43	1512	1.1	1.5	0.9–2.3
Atopic dermatitis					
No	53	2276	1	1	Reference
Yes	13	418	1.4	1.6	0.8–3.0

ORc, Crude Odds Ratio; Ora, Odds Ratio adjusted by gender, age and country; C.I. 95%, Confidence Interval 95% related to the ORa. Missing data on infection or dermatitis were excluded.

The study was carried out in accordance with the requirements of the Ethics Committees and Data Inspectorates in each of the participating countries or regions.

3. Results

Most of the cases (96 of the 118) that were accepted as definitive or possible by the reference pathologist came from Spain, France and Italy (Table 1). Data regarding only the definitive cases were used in the following tables.

The age distribution is shown in Table 3. Among the MF cases, 52.6% were males. We used 2904 controls

Table 3
Characteristics of the cases of MF and controls that were interviewed

Selected characteristics	Cases		Controls	
	Definite		Control	
	$n=76$	(%)	$n=2904$	(%)
Age groups (years)				
35–50	23	(30)	1046	(36)
51–60	18	(24)	850	(29)
61–65	18	(24)	561	(19)
66–69	17	(22)	447	(15)
Gender				
Male	40	(53)	1965	(68)
Female	36	(47)	939	(32)
Reported diseases				
Mumps (ever had)	39	(48)	1493	(45)
Mumps confirmed	*32*	(*84*)	*1042*	(*70*)
Herpes (ever had)	7	(9)	264	(8)
Herpes confirmed	*6*	(*86*)	*249*	(*94*)
Hepatitis (ever had)	9	(11)	251	(8)
Hepatitis confirmed	*8*	(*10*)	*208*	(*6*)
Urticaria (ever had)	9	(11)	216	(7)
Urticaria confirmed	*5*	(*56*)	*161*	(*76*)

Only patients that answered 'yes' were included in the table. The disease confirmed had been diagnosed by a medical specialist and their % is calculated in relation to the total of the patients that answer yes for this disease in the interview.

Table 4
Odds ratios (ORs) for MF according to specific diseases which subjects have ever had 5 years prior to the interview (in definitive and possible cases)

	Cases definite ($n=76$)	Controls ($n=2904$)	OR definite Ora	C.I. 95%
Mumps				
No	21	869	1	
Yes	32	1042	1.8	1.0–3.0
Herpes				
No	67	2589	1	
Yes	3	187	0.6	0.2–1.8
Hepatitis				
No	67	2607	1	
Yes	8	208	1.6	0.7–3.3
Liver cirrhosis				
No	75	2852	1	
Yes	0	8	–	–
Asthma				
No	69	2656	1	
Yes	6	160	1.6	0.7–3.8
Urticaria				
No	65	2630	1	
Yes	5	172	1.4	0.6–3.6
Diabetes				
No	70	2715	1	
Yes	2	74	0.9	0.2–3.7
Psoriasis				
No	59	2739	1	
Yes	11	89	7.2	3.6–14.5
Bone diseases[a]				
No	61	2459	1	
Yes	10	292	0.8	0.4–1.6
Typhus				
No	74	2793	1	
Yes	1	78	0.4	0.1–2.5
Thyroid diseases[a]				
No	72	2654	1	
Yes	1	135	0.3	0.1–1.7
Gallstones				
No	64	2613	1	
Yes	8	139	0.9	0.7–1.7
Inflammatory gall bladder				
No	65	2740	1	
Yes	6	68	2.2	0.7–7.4
Fractures				
No	57	2003	1	
Yes	16	714	0.8	0.5–1.4
Head injury				
No	706	2582	1	
Yes	6	322	1.0	0.5–2.5
Other diseases				
No	14	304	1	
Yes	40	1078	1.4	0.7–2.7
Inflammatory bowel disease				
No	73	2768	1	
Yes	3	54	2.4	0.8–8.0

OR adjusted by age, gender and country (regional stratum).
[a] Diseases in relation to this structure or organs.

and excluded 1670 because they were outside of the age range of MF cases or did not agree to the interview.

Mumps, past and present, were the most frequently reported diseases as (Table 3). A confirmed diagnosis indicated that the diagnosis was made by a physician.

Table 2 shows the crude ORs for a history of the most frequently reported infections (mumps, herpes or hepatitis) and atopic dermatitis 5 years before the diagnosis of MF among the definitive cases. MF patients reported more dermatitis, although the association was not statistically significant, (OR 1.6, 95% CI: 0.8–3.0).

Table 4 shows that the highest ORs for MF were found for people with psoriasis (OR 7.2, 95% CI: 3.6–14.5). Urticaria patients had an OR for MF of 1.4, 95% CI: 0.6–3.6.

None of the infectious diseases was significantly associated with MF (Tables 2 and 3). Other diagnoses occurred in too few numbers (less than 3 exposed cases) to make quantitative estimates meaningful.

4. Discussion

MF correlates to psoriasis, herpes infection and dermatitis atopica. These diseases could be risk factors for MF, part of a common aetiology behind the disease and MF, or simply part of the early diagnostic pattern for MF.

Despite some limitations, such as possible diagnostic misclassification, that has been described by other authors [9,13], our study provides evidence for an increased risk of MF among patients with psoriasis (OR 7.2) 5 years before the diagnosis of MF. The diagnosis of psoriasis was based on histology or clinical presentation, or both. This would strongly suggest that these skin conditions were precursor lesions belonging to a cutaneous lymphoma. Studies of nationwide series [13] of psoriasis patients from Sweden provide evidence against an increased risk of melanoma. In addition to non-melanoma and genital cancer, patients hospitalised for psoriasis were at an increased risk of several malignancies, in particular those associated with alcohol drinking and tobacco smoking. MF is also described in relation to these risk factors [12].

In 1974, Tan and colleagues proposed that persistent antigenic stimulation may play a role in MF [14]. Herpes and dermatitis have been suggested as possible stimulants. Our results do not contradict this hypothesis, but our empirical evidence is weak [8,15,16].

The classical MF presentation of CTCL progresses through four phases, ranging from the premycotic stage to the tumour phase [17]. In the present study, major efforts were made by the pathologist to exclude uncertain cases. The initial diagnosis was reassessed by a single expert and based upon strict criteria. These measures served to increase the internal validity of the study, since

there can be significant intraobserver variability in the pathological interpretation of the same specimens [18].

The controls for the Spanish patients were not chosen at random for the population, but were selected from an age-, gender- and hospital population area-matched group of patients with incident colon cancer. An analysis of the data between the population and colon cancer controls showed no differences.

Dermatitis could be associated with MF due to CTCL cells entering the skin, followed by epidermotropism [19,20] in the early stages of the disease. In more advanced stages of CTCL, MF cells lose their dependence on epidermal cell adhesion molecules and cytokines, which result in their epidermotropism either being diminished or lost entirely. Accordingly, defined, but incident, cases could represent early stages of the disease.

An association between a skin disease and MF may be causal, and the causal direction could be from the disease to MF or from early stages of MF to the disease. The association may also be due to overdiagnosis as a result of more intense surveillance of MF patients with skin lesions related to their MF, which increases the risk of detection bias [2,6,15]. Misclassification of MF is probably a major problem in this study because it mimics several benign skin disorders, including eczema, psoriasis and contact dermatitis [9]. For this reason, we only included in this study incident cases of MF, and in order to reduce the magnitude of this bias, we only included diseases reported to be present 5 years before MF was diagnosed. The large number of missing data for the analysis should also be taken into consideration when interpreting the results.

The weak association with herpes infection could support a retrovirus as the mechanism underlying the disease [6,20,21], although infection is the primary cause of mortality in patients with cutaneous T-cell lymphoma [9]. This would be in accordance with the hypothesis of a failure in the Langerhans' cells and the activate resting macrophages which respond by releasing a complex mix of cytokines active on keratinocytes, fibroblasts and endothelial and lymphohematopoietic cells [22–24].

The association we find with diabetes has not been reported before and could be explained by the immunological nature of the neoplastic cells responsible for this disorder, but further studies are necessary.

The reported associations in this paper are probably of a non-causal nature, but may serve as risk indicators for further clinical work.

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Appendix

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