

Cutaneous Lupus Erythematosus: Epidemiology, Association with Systemic Lupus Erythematosus and Comorbidity

CARINA GRÖNHAGEN

Department of Dermatology, Karolinska Institutet, Danderyd Hospital, SE-182 88 Stockholm, Sweden.

E-mail: carina.gronhagen@ds.se

At the 27th of January 2012, Carina Grönhagen defended her thesis at Danderyds Hospital, Stockholm, Sweden. Faculty opponent was Professor Chris Andersson, Department of Dermatology and Venereology, Linköping University. Main supervisor was Associate Professor Filippa Nyberg, and assistant supervisor was Associate Professors Fredrik Granath and Michael Fored.

Lupus erythematosus (LE) is a chronic disease that includes a broad spectrum of symptoms. Lupus is Latin for wolf; perhaps the skin lesions were thought to resemble wolf bites. LE is included among the connective tissue diseases and is divided into systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE). These can occur together or separately. The classification of CLE was difficult and confusing until two American dermatologists (Gilliam and Sontheimer) devised a new improved classification that gained wide acceptance. According to Gilliam and Sontheimer, the cutaneous manifestations of LE can be divided into LE-specific and LE-non-specific skin manifestations based on histopathological findings. LE-specific skin manifestations show a typical histopathological picture with a lichenoid tissue reaction (interface dermatitis). LE-specific skin manifestations can be further subdivided into acute CLE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE), where classic discoid LE (DLE) is the most common form.

Earlier epidemiological research into CLE has been hampered by a shortage of case ascertainment, and much of our knowledge is based on rather small and often retrospective studies. Because of the Swedish Health Care Registers, we have now been able to study larger groups of CLE patients based on information collected prospectively. This thesis is based on 4 studies, each described briefly below.

Cutaneous manifestations are very common in SLE patients (over 80% display skin symptoms sometime during the course of the disease, and in 20–25% of patients cutaneous manifestations are the first symptom of SLE disease). Four of the 11 American College of Rheumatology (ACR) criteria used for SLE classification are mucocutaneous (malar rash, discoid lupus, photosensitivity and oral ulcers). Not all of these criteria are well-defined and they are often difficult to distinguish from other common skin diseases. In the first study we wanted to assess the frequency of cutaneous manifestations according to Gilliam and Sontheimer's classification in a cohort of 260



Fig. 1. Carina Grönhagen defended her thesis at Stora Aulan, Danderyds Hospital.

patients with SLE. Our aim was also to compare clinical and serological characteristics in SLE patients with and without CLE. We also aimed to investigate the agreement between dermatologists and rheumatologists concerning the ACR criterion malar rash. All patients were enrolled at the Department of Rheumatology, Karolinska University Hospital, all of which fulfilled at least 4 of the revised ACR criteria for SLE. Examination by a dermatologist showed that LE-non-specific cutaneous manifestations were present in 43% of the patients and LE-specific in 23%. Of the LE-specific, DLE (11%) was the most common, followed by SCLE (8%) and ACLE (4%). Of the LE-non-specific skin manifestations, Raynaud's phenomenon was the most common (25%), followed by non-scarring alopecia (9%) and vasculitis (8%). The main serological findings were that Ro/SSA, La/SSB autoantibodies and rheumatoid factor were all significantly more frequent in SLE patients with CLE than in those without CLE. β 2GP1, on the other hand, was significantly more common in SLE patients without CLE. We found agreement between dermatologists and rheumatologists

in the diagnosis of malar rash in just 60%; corresponding to a kappa-coefficient of 0.35.

There are no earlier large, population-based studies reporting the incidence of CLE and its different subsets as well as the association between CLE and SLE. The second study was a population-based cohort study, in which we aimed to calculate the overall incidence rate of CLE as well as the age- and gender-specific incidence of CLE and its subsets and assess the short-term probability of receiving an additional diagnosis of SLE. A total of 1,088 patients were registered with CLE in 2005–2007 in the Swedish National Patient Register (NPR). The mean annual incidence of CLE was 4.0/100,000 (95% confidence interval (CI) 3.9–4.2), i.e. approximately 380 people are diagnosed with CLE each year in Sweden. The female to male ratio was 3:1 and mean age 54 years. DLE was the most common subset (80%). Of the newly diagnosed patients with CLE almost one-quarter (24%) had a previous known SLE diagnosis. The Kaplan–Meier estimates show that the probability of receiving an additional diagnosis of SLE was 18.1% (95% CI 14.1–22.1) during the first 3 years after being diagnosed with CLE.

Previous epidemiological studies have shown that patients with SLE and other autoimmune diseases, such as rheumatoid arthritis, have increased morbidity and mortality from cancer. There are more than 100 published case reports of DLE and squamous cell carcinoma in lesional skin and SCLC has been associated with various internal cancers. The aim of study III was to estimate the overall and specific cancer risks in a nationwide population-based cohort of patients diagnosed with CLE and compare those with a matched control cohort derived from the general population without a diagnosis of CLE. We also wanted to investigate the history of cancer for CLE patients before they were diagnosed with CLE and also determine what influence comorbidity with SLE had on cancer risk.

A cohort of 3,663 individuals was diagnosed with CLE in the NPR (1997–2007). As a comparison group, we identified a matched control cohort of 10,989 individuals (3 controls for each CLE case) from the general population that was not diagnosed with CLE. The control cohort was individually matched for possible confounders (age, gender and geographical region). Both the CLE cohort and the control cohort were then linked with the Cancer Register and the Cause of Death Register to identify all cancers diagnosed in the period 1958–2007 and obtain information on death. A significantly increased cancer risk was found in the CLE cohort (hazard ratio (HR) 1.8; 95% CI 1.5–2.2) with 183 incident, individual cancers occurring during follow-up. The most increased risk estimates were found for buccal cancer (HR 5.4; 95% CI 1.8–16.1), accompanied by an approximately 4 times increased risk for lymphomas (HR 4.4; 95% CI 1.8–10.7), respiratory



Fig. 2. Opponent Professor Chris Andersson.

cancer (HR 3.8; 95% CI 2.2–6.4) and non-melanoma skin cancer (NMSC) (HR 3.6; 95% CI 1.8–7.2). The risk estimates remained elevated when we excluded patients who were also diagnosed with SLE. Although no causal relationship between potential risk factors and cancer development in CLE patients could be established in this study, smoking is probably a substantial confounder, in that CLE patients have been shown to smoke more than the general population. Other possible explanations could be that CLE patients are more sensitive to ultraviolet (UV)-light and certain virus infections (for example HPV).

More than 125 case reports of drug-induced SCLC have been published and more than 40 drugs with diverse latencies have been involved, but large observational studies are lacking. The aim of this study was therefore to examine the association between exposure to certain suspected drugs (previously reported as possible triggers) and the subsequent development of SCLC in a large group of incident SCLC cases. We performed a population-based matched case-control study that included all individuals registered with a SCLC diagnosis for the first time during 2006–2009 in the NPR. For all incident SCLC cases, 10 controls from the general population were matched individually for age, gender and county of residence. A total of 234 SCLC patients were enrolled, together with 2,311 matched controls. They were then linked to the Prescribed Drug Register in order to determine information on drug exposure of the *a priori* suspected drugs 0–6 months before SCLC diagnosis. Exposure to terbinafine and tumour necrosis factor alpha (TNF- α) inhibitors 0–6 months before SCLC diagnosis

showed the greatest increase in risk (odds ratio (OR) 52.9 (95% CI 6.6–∞) and OR 8.0 (95% CI 1.6–37.2), respectively) for a subsequent diagnosis of SCLE. No increased risks were found when other systemic antimycotics were investigated. Exposure to anti-epileptic and proton pump inhibitors (PPIs) 0–6 months before SCLE diagnosis showed approximately three-fold elevated risk estimates and two-fold elevated risks were seen for thrombocyte inhibitors, angiotensin-converting-enzyme (ACE)-inhibitors and non-specific anti-inflammatory drugs (NSAIDs). The analysis was repeated after excluding SCLE cases previously diagnosed with SLE. However, no significant

changes in the estimates were found. Approximately one-third of all SCLE cases can be attributed to previous drug exposure.

This thesis adds to previous knowledge about epidemiology, disease progression to SLE, comorbidity and the association with certain drugs in CLE. Swedish population-based epidemiological data on CLE will potentially be useful in the planning of healthcare as well as clinical trials. For prospective studies, especially of the intermediate group between CLE and SLE, population-based quality registers will be needed to further improve healthcare for patients with CLE.