patients had died (33%). Among the patients who died, only two died of the disease. The other four patients died of COVID-19, brain haemorrhage (after a fall), acute leukaemia and immune thrombocytopenic purpura associated with chronic lymphocytic leukaemia. Estimated median overall survival (OS) was 24·1 months (95% CI 16·4–31·8) and disease-specific OS was not reached.

We observed 33% (n = 6) adverse events (AE) in six different patients: four grade 2 AEs (psoriasis, asthenia, bullous pemphigoid and liver toxicity), one grade 3 AE (hepatitis) and one grade 5 AE (death as a result of immune thrombocytopenic purpura).

Our data confirm the results of phase II data evaluating immune checkpoint inhibitors[1,3–5] in advanced cSCC, in a real-world setting. In contrast to previous phase I and II trials,[1,3,5,6] we observed a higher ORR (67% vs. 41–50%), although our series included a majority of stage IV cSCC. A recent real-world study reporting data about anti-PD1 antibodies in cSCC, which included eight patients treated with CEMI, reported an ORR of 59%.[7] It is remarkable to notice that patients are older in real-world studies compared with trials. Furthermore, patients over 60 years old and patient who were immunocompromised with chronic lymphocytic leukaemia may respond to CEMI. This may be related to a high tumour mutational burden, associated with increased immunogenicity, commonly observed in the tumours of older patients.[8]

In terms of safety, CEMI was overall well-tolerated, with about 10% of patients discontinuing therapy because of toxicity.[7] AEs were less frequent than previously reported in trials,[1,3] which may be explained by the retrospective nature of the study.

In conclusion, our data confirm the efficacy and safety of CEMI for the treatment of patients with advanced cSCC in a real-world setting, including older patients and individuals who are immunocompromised. Owing to the durable nature of the responses and the lack of treatment alternatives, CEMI should be considered as first-line treatment in advanced cSCC.[9]

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Male patients with rosacea have increased risk for migraine: a population-based study

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Dear Editor, Previous reports have demonstrated an association between rosacea and migraine.[1] This relationship has been found in postmenopausal women, particularly in large registry studies, but also in some smaller clinical studies.[1] A nationwide study (n = 49 475) from Denmark reported that female patients with rosacea who were aged > 50 years had a 1·3-fold increased risk for migraine.[2]

We studied the association between rosacea and migraine in the general population of the Northern Finland Birth Cohort 1966 Study (NFBC66), which is a longitudinal research programme based in the two northernmost provinces in Finland. The whole NFBC66 cohort has been evaluated regularly since birth by means of health questionnaires and clinical examinations. In connection with a 46-year follow-up survey, a total of 3181 persons living in a given geographical area (in the city of Oulu and within 100 km of the city, including rural areas) were asked to attend a clinical examination, which included a whole-body examination performed by dermatologists; 1932 of them responded (60·7%). Overall, 53·7%

Table 1 The association between rosacea and the symptoms of migraine stratified by sex

Positive answer for the question		Men				Women			
		Total (n)	n (%)	OR (95% CI)	Adjusted OR (95% CI)	Total (n)	n (%)	OR (95% CI)	Adjusted OR (95% CI)
'I have a doctor-diagnosed migraine'	Rosacea	90	15 (16·7)	2·01 (1·10–3·70)	**2·26 (1·13–4·53)**	194	46 (23·7)	0·82 (0·57–1·19)	0·86 (0·57–1·30)
	Control	764	69 (9·0)	Reference	Reference	806	221 (27·4)	Reference	Reference
'Physical activity increases my headache and I have to rest when I have headache'[a]	Rosacea	91	11 (12·1)	1·65 (0·83–3·27)	1·83 (0·86–3·90)	194	39 (20·1)	1·01 (0·68–1·50)	0·99 (0·64–1·53)
	Control	768	59 (7·7)	Reference	Reference	809	161 (19·9)	Reference	Reference
'My headache prevents me from doing daily activities'[a]	Rosacea	90	15 (16·7)	2·03 (1·10–3·72)	**2·22 (1·12–4·37)**	194	44 (22·7)	0·83 (0·57–1·20)	0·91 (0·60–1·38)
	Control	768	69 (9·0)	Reference	Reference	807	211 (26·2)	Reference	Reference
'My headache is often one-sided'[a]	Rosacea	91	19 (20·9)	2·14 (1·23–3·73)	**2·07 (1·09–3·94)**	193	55 (28·5)	1·08 (0·76–1·53)	1·14 (0·77–1·69)
	Control	766	84 (11·0)	Reference	Reference	810	218 (26·9)	Reference	Reference
'My headache is often throbbing'[a]	Rosacea	91	21 (23·1)	1·59 (0·94–2·69)	**1·83 (1·00–3·33)**	194	78 (40·2)	1·26 (0·92–1·74)	1·31 (0·91–1·90)
	Control	769	122 (15·9)	Reference	Reference	809	281 (34·7)	Reference	Reference
'My headache is related to nausea'[a]	Rosacea	91	3 (3·3)	0·56 (0·17–1·84)	0·60 (0·18–2·05)	192	38 (19·8)	1·01 (0·68–1·50)	1·07 (0·69–1·66)
	Control	766	44 (5·7)	Reference	Reference	799	157 (19·7)	Reference	Reference
'Bright lights and loud voices irritate me when I have headache'[a]	Rosacea	91	18 (19·8)	1·58 (0·90–2·75)	**1·94 (1·03–3·62)**	193	65 (33·7)	0·94 (0·67–1·31)	0·99 (0·68–1·44)
	Control	762	103 (13·5)	Reference	Reference	805	283 (35·2)	Reference	Reference
'My headache is related to menstruation'[a]						194	44 (22·7)	0·75 (0·52–1·09)	0·72 (0·47–1·09)
						807	226 (28·0)	Reference	Reference

OR, odds ratio; CI confidence interval. Adjusted for education, physical activity, regular tension neck pain, body mass index based on World Health Organization classification and smoking status. As there was an interaction between sexes the associations are reported by sex. [a]These questions were used to define the symptoms of migraine without aura according to The International Classification of Headache Disorders, 3rd edition (beta version). Values in bold indicate statistical significance.

(n = 1036) of these participants were women and 46·3% (n = 896) were men.[3] Diagnosis and classification of rosacea was based on the evaluation by a dermatologist at the study visit[3] and on the internationally accepted criteria.[4] Rosacea was classified using the following four subtypes according to its clinical presentation: erythematotelangiectatic rosacea (ETR), papulopustular rosacea, phymatous rosacea and ocular rosacea.[4] Patients self-reported information regarding doctor-diagnosed migraine. The symptoms relating to migraine were gathered using specific questions [the symptoms of migraine without aura according to The International Classification of Headache Disorders, 3rd edition (beta version)] (see Table 1 for questions).[5]

The prevalence of rosacea was 15·1% (n = 292); 10·5% for men (n = 94) and 19·1% for women (n = 198). Subtypes of rosacea were divided as follows: ETR 83·2% (n = 242), papulopustular rosacea 15·4% (n = 45), ocular rosacea 0·3% (n = 1) and phymatous rosacea 0·1% (n = 3). The prevalence of self-reported migraine in the whole cohort was 21·5% (n = 61) among those with rosacea and was 18·5% (n = 290) among those without (P = 0·2). The patients with rosacea had more one-sided [25·3% (n = 74)] and throbbing headache [33·9% (n = 99)] when compared with those without rosacea [18·4% (n = 301) and 24·6% (n = 402), respectively] (P < 0·01). Those with rosacea more often had several simultaneous symptoms relating to migraine than those without rosacea (P < 0·01, data not shown). Using logistic regression analyses we found that male patients with rosacea had a two-fold higher risk for self-reported migraine, for 'one-sided and throbbing headache', 'headache that prevents doing daily activities' and for 'headache that is irritated by bright lights and loud voices'. A corresponding association was not seen in female patients (Table 1). Those with papulopustular rosacea experienced migraine symptoms more often than patients with the ETR subtype, but the difference was not statistically significant (P < 0·8) (data not shown).

The exact pathophysiology of rosacea remains unknown.[6] In addition to genetic predisposition, impairment in epidermal barrier and dysregulation of the immune system, rosacea is characterized by neurovascular dysregulation and neurogenic inflammation, thus sharing similar pathomechanisms with migraine.[6,7] Furthermore, in both rosacea and migraine, symptoms (such as episodes of flushing, erythema, telangiectasia, headache, photophobia and phonophobia) are presented mainly in the area innervated by the trigeminal nerve.[6,7] Thus, changes in facial blood flow and neuroinflammation have been considered to suggest a possible relationship between these two diseases.[6]

Previously, contrary to our results, the association between rosacea and migraine has been shown primarily in female patients.[1,2] Previous studies have mostly based their findings on registry data, which may have caused selection bias and prevented the discovery of migraine risk in men. The main strength of registry studies is the use of large datasets. However, individuals with mild symptoms who do not seek help from a physician can be missed. Thus, men who are less eager to seek help for their disease may have been omitted. Furthermore, in database studies, it is usually not possible to differentiate between rosacea subtypes or take confounding factors into consideration.

The major strength of our study is a pure general population. Study cases were not selected for the study and both sexes were represented almost equally. Furthermore, the diagnosis of rosacea was evaluated by dermatologists and subtypes of rosacea were reported. The migraine or headache symptoms were surveyed using multidisciplinary questions. The setting of the cohort study made it possible to take several confounding factors into consideration. One limitation of this study is that not all study cases who were invited chose to participate. In addition, diagnosing ETR is especially difficult as the diagnosis is solely clinical.[8]

Based on our findings, we recommend that physicians who encounter patients with rosacea, especially male patients, ask them about migraine symptoms while simultaneously ensuring the exact diagnosis of rosacea subtype.[8]

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Lymph node and visceral progression without erythroderma or blood worsening in erythrodermic cutaneous T-cell lymphoma: nine cases

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Dear Editor, The prognosis of erythrodermic cutaneous T-cell lymphomas (ECTL) depends on lymph node (N) and visceral (M) involvement, and blood stage (B). Blood involvement is determined by circulating Sézary cells, identified on peripheral blood immunophenotyping, and is staged as B0 (absolute count < 250 cells mm^{-3}), B1 (250–1000 cells mm^{-3}) or B2 (Sézary syndrome; ≥ 1000 cells mm^{-3}). Sézary syndrome is the most common subtype of ECTL and has a 5-year overall survival rate of 36%.[1] Other prognostic markers include male sex, age > 60 years, an elevated rate of lactate dehydrogenase (LDH), and histological large cell transformation (LCT).[1–3] ECTL progression is usually homogeneous and simultaneously involves all compartments of the disease. We report nine patients with B1 or B2 stage ECTL displaying an unusually discrepant outcome profile with the rapid onset of nodal or visceral involvement contrasting with the lack of progression of cutaneous and blood involvement.

We retrospectively identified cases from dermatology departments of the French Cutaneous Lymphoma Study Group (GFELC). Inclusion criteria were initially B1 or B2 ECTL featuring nodal or visceral progression during follow-up, while erythroderma and circulating Sézary cells (remaining in B0 or B1 stage) were controlled. Clinical and biological data were collected (characteristics of the ECTL at diagnosis, treatments, characteristics of the progression, outcome), and biopsies available at progression were reviewed.

Nine patients were included (five women and four men), with a median age of 65 years (range 49–79) at ECTL diagnosis. The European Organisation for Research and Treatment of Cancer–International Society for Cutaneous Lymphomas stage was IVA1 for seven patients and IIIB for two. Except for one patient with mastocytosis treated with imatinib (#6), no patient had a significant medical history. At diagnosis of ECTL, only one patient displayed an enlarged node > 1·5 cm (not biopsied), and the median number of Sézary cells was 1440 per mm^3 (range 396–4930). Eosinophilia was present in one patient (#3, 1000 cells mm^{-3}) and elevated LDH in four. By applying the prognostic index of Scarisbrick *et al.*,[3] the risk evaluation was low for two, intermediate for four and high for three patients.

The median time to progression was 41 months (range 12–67), after a median of three (range 1–11) previous treatment lines (Table 1). The progression involved lymph nodes in five patients and nodes plus other organs in four. Among patients with visceral progression, three had meningitis and one had a major splenomegaly. Four patients had simultaneous skin tumours. The median number of Sézary cells at progression was 250 per mm^3 (range 20–840). At progression, the LDH rate was elevated in eight patients, monocytosis was present in five (median count 2480 cells mm^{-3}, range 1010–5300) and eosinophilia was present in five (median count 5330 cells mm^{-3}, range 470–20 000] (Table 1).

Pathological data at progression were reviewed for eight patients: skin biopsy (four patients), node biopsy (five patients) and cerebrospinal fluid (one patient). LCT was observed in six patients, with significant expression of CD30 (> 10%) in only one case. One case had histological and phenotypic features reminiscent of angioimmunoblastic T-cell lymphoma (Table 1).

Upon progression, seven patients received polychemotherapy (median one line, range 1–4), while one (#9) was successfully treated with mogamulizumab (still in response 1 year after progression) and one did not receive any treatment because of rapid worsening. Eight patients died, within a median time of 12 weeks (range 4–52) after the diagnosis of progression, six from lymphoma, one from infection and one from haemophagocytic syndrome.

We report a case series of nine patients with ECTL with nodal progression with or without visceral progression while skin and blood involvement were controlled. Biopsy of new tumour sites appearing at progression was associated with LCT in six cases. In our patients, we could not identify noticeable epidemiological, clinical, biological or histological features at diagnosis that could predict this evolution. Applying a prognostic index[3] was also not predictive of the evolution. Only one patient had eosinophilia at baseline, compared with five at progression. Eosinophilia was previously shown to be an independent unfavourable prognostic factor in cutaneous T-cell lymphomas.[4] Furthermore, five patients displayed monocytosis at progression. Monocytosis is associated with a poor survival in peripheral T-cell lymphomas,[5] with no reports in cutaneous T-cell lymphomas. Those cells could inhibit antitumour responses, as the detrimental influence of monocytic myeloid-derived suppressor cells has been described in cancers.[6]

Such an atypical evolution has rarely been reported. Michaelis *et al.* described four patients with Sézary syndrome who experienced a transformation into 'pleomorphic T-cell lymphoma' in the lymph nodes, after an average of 43 months. All of those patients died.[7] LeBlanc *et al.* reported four patients with mycosis fungoides or Sézary syndrome who developed, within 1–5 years, nodal involvement mimicking angioimmunoblastic T-cell lymphoma.[8]