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Rosacea and perioral dermatitis: a single-center retrospective analysis of the clinical presentation of 1032 patients

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Summary

Background: Rosacea is a common chronic inflammatory cutaneous disorder affecting nearly 5.5 % of the adult population. Our aim was to evaluate the prevalence and epidemiology of rosacea and perioral dermatitis (POD) in an ambulatory care setting.
Methods: We retrospectively analyzed medical data of patients with a confirmed diagnosis of rosacea or perioral dermatitis (POD) presenting at our university hospital outpatient clinic during a 3-year period.
Results: Out of 1032 patients, 81.5 % were diagnosed with rosacea and 18.5 % with POD. Overall prevalence was 1.4 % for rosacea and 0.3 % for POD. 69.3 % of the analyzed patients were female. Overall mean age was 49.3 ± 7.7 (1–92) years; the women's average age was less than the men's. Patients with POD were younger and predominantly female, whereas patients with phymatous rosacea were older and predominantly male. The most common phenotypes were papulopustular rosacea (68.4 %), erythematotelangiectatic rosacea (22.5 %), and phymatous rosacea (8.0 %). Special forms of rosacea were diagnosed in 15.8 % of the patients; the most frequent were ocular rosacea (6.9 %) and steroid-induced rosacea (5.4 %).
Conclusions: The large patient cohort analyzed in our study provides a good estimate of the frequency of the rosacea subtypes, special forms and of perioral dermatitis in a hospital-based outpatient care setting.

Introduction

Rosacea is a common cutaneous disorder that primarily affects the central face, and is most frequently observed in individuals with lightly pigmented skin [1, 2]. Current epidemiological data related to rosacea is scarce and partially controversial. The prevalence of rosacea is difficult to assess due to inconsistent definitions, variable clinical manifestations and the wide range of skin diseases that exhibit similar clinical features, as well as cultural and social perceptions of the disease [3, 4]. A multicenter, cross-sectional study from 2016 reported a prevalence of 5 % and 12 % for Russia and Germany, respectively [5]. A recent meta-analysis estimates the overall global prevalence of rosacea in the adult population at 5.46 % [6].

However, a limiting factor is the lack of a commonly accepted international classification that describes the different forms of rosacea accurately without leaving a broad scope for interpretation. Because rosacea patients often present with a wide range of skin symptoms and various clinical presentations, precise clinical classification is often challenging [7].

Most studies concerning the different forms of rosacea have used a subtype-oriented classification. Based on current scientific knowledge and morphologic characteristics, a global assessment has distinguished four main subtypes (S. 1–4): erythematotelangiectatic (ETR, S. I), papulopustular (PPR, S. II), phymatous (S. III) and ocular rosacea (S. IV), which is an ocular manifestation of rosacea that involves the eyelids and the front of the eye, and includes blepharitis, conjunctival hyperemia, and rosacea-associated keratitis [8].

However, the latest attempts towards an approach based on phenotype rather than subtype to the diagnosis and classification of rosacea are linked to our increased understanding of disease pathophysiology, and have received international acceptance [7, 9, 10]. Rosacea may begin with a transient, primarily centrofacial erythema. It can also present as an ETR (severity grade I), as a PPR (severity grade II), or as a glandular/hyperplastic form (phymatous rosacea, severity grade III). Since the diagnosis is generally clinically determined, it is crucial that physicians consider the differential diagnoses (DDs) for each of the severity forms, such as carcinoid syndrome, menopause-induced flushing, UV-induced cutaneous vascular damage (DD: transient erythema), polycythemia vera, lupus erythematosus (DD: ETR), papulopustular acne, perioral dermatitis (DD: PPR), lupus pernio and eosinophilic granuloma (DD: glandular/hyperplastic rosacea). These phenotypes can occur isolated or in combination [9, 11, 12]. Furthermore, rosacea can present with abnormal or unusual symptoms and progression. These special forms include ocular rosacea, steroid-induced rosacea, rosacea fulminans, granulomatous rosacea, Morbihan disease, gram-negative rosacea, rosacea conglobata, and pediatric rosacea [11, 12]. Data concerning the distribution of the special forms is rare and the prevalence of each of these forms is still unclear.

Additionally, patients with perioral dermatitis (POD) can present with symptoms similar to those of rosacea and complicate differentiation from rosacea's special forms.

Therefore, a thorough analysis of a large cohort of rosacea patients presenting in the outpatient clinic of the Department of Dermatology and Allergy of the Ludwig-Maximilian-University (LMU) might contribute to a better understanding of the epidemiology of rosacea in a clinical setting, especially concerning the phenotypes and special forms of the disease.

Material and methods

Ethics

This study was approved by the ethics committee of the medical faculty of the LMU, Munich, Germany (Ref.-No. 080-14) and complies with the principles of the Declaration of Helsinki. Patient information and identification were kept confidential at all times and the data analysis was performed anonymously.

Inclusion criteria

Patients' data were collected from the digital files of the Dermatology Department of the LMU. Our inclusion criteria comprised patients with a confirmed diagnosis by ICD-

10 code (L71.0 for perioral dermatitis [POD], L71.1 for rhinophyma, L71.8 for other forms of rosacea, and L71.9 for unspecified forms of rosacea). Patients were recruited between Jan 1st, 2012 and Dec 31st, 2014. They were selected independently of age, gender, or origin.

Exclusion criteria

Since some of the patients had several consultations during the period from 2012–2014, only the first consultation of each patient was considered for further analysis in order to eliminate bias.

Statistics

Standard descriptive statistics such as the mean, standard deviation and standard error of the mean were calculated with statistics software (SPSS version 22, IBM, NY/USA).

Results

Patients

Of the 1032 included patients, 841 (81.5 %) had been diagnosed with rosacea (ICD-10 L71.1, L71.8 or L71.9) and 191 (18.5 %) with perioral dermatitis (POD, ICD-10 L71.0). The prevalence of patients with rosacea was 1.4 % ($n_{rosacea}/n_{total}$ = 841/60,965) and 0.3 % (n_{POD}/n_{total} = 191/60,965) for POD of all treated patients during that period of time.

Age and Gender

The mean age of all patients was 49.3 ± 17.7 (1–92) years. Children (< 18 years old) comprised only 0.8 % (n = 8) of the analyzed cohort. Patients who presented with rosacea were slightly older than average (51.6 ± 17 [1–92] years) while those diagnosed with perioral dermatitis were approximately eleven years younger than the overall average (38.7 ± 17.3 [1–77] years). When compared by gender, female patients who received either of these diagnoses tended to present earlier (48.5 ± 17.7 [1–92] years) than male patients (50.9 ± 17.8 [1–86] years).

Patients presenting with phymatous rosacea and ocular rosacea were diagnosed at a notably higher mean age than the overall average, respectively at 60.3 ± 14.3 (26–84) and 54.0 ± 17.7 (15–82) years old. However, the average age of the remaining special forms of rosacea was lower than the mean of the total study cohort (49.3 ± 17.7 [1–92] years) (Table 1).

Overall, 715 (69.3 %) of all patients were female, of which only five (0.7 %) were pregnant or breastfeeding. This percentage was slightly less in patients with rosacea

Table 1 Distribution of rosacea, POD, phenotypes (severity-oriented) and special forms related to sex and age. The table sums up the main results of the study and gives an overview of the general distribution of the phenotypes and special forms of rosacea, divided into total number of patients, gender and mean age.

General distribution	Patients n (%)	Female n (%)	Mean age Years
Total	1032 (100)	715 (69.3)	49.3 ± 17.7 (1–92)
Rosacea	841 (81.5)	543 (64.6)	51.6 ± 17.0 (1–92)
POD	191 (18.5)	172 (90.1)	38.7 ± 17.3 (1–77)
Severity of phenotypes			
Rosacea diathesis (transient erythema)	11 (1.1)	7 (63.6)	46.3 ±15.3 (22–76)
ETR	219 (22.5)	160 (73.1)	52.4 ± 17.7 (15–86)
PPR	667 (68.4)	490 (73.5)	47.0 ± 17.5 (0–92)
Phymatous rosacea	78 (8.0)	22 (28.2)	60.3 ± 14.2 (26–84)
(975 documented phenotypes)			
Special forms			
Ocular rosacea	69 (6.9)	49 (71.0)	54.0 ± 17.7 (15–82)
Rosacea conglobata	2 (0.2)	1 (50.0)	40.5 ± 6.4 (36–45)
Rosacea fulminans	8 (0.8)	6 (75.0)	48.4 ± 17.1 (27–75)
Gram-negative rosacea	1 (0.1)	1 (100)	42 ± 0 (42)
Steroid-induced rosacea	54 (5.4)	42 (77.8)	42.4 ± 19.5 (1–81)
Granulomatous rosacea	14 (1.4)	7 (50.0)	43.9 ± 17.7 (21–86)
Morbihan disease	10 (1.0)	6 (60.0)	43.4 ± 11.4 (25–60)
Rosacea in children	8 (0.8)	4 (50.0)	5.4 ± 4.8 (1–13)
(166 documented special forms in 158 patients)			

(64.6 %, n = 543/841), but was much higher in patients with POD (90.1 %, n = 172/191). In contrast, when the severest form of rosacea was investigated, patients diagnosed with phymatous rosacea were predominantly male (71.8 %, n = 56/78) (Table 1).

Clinical Symptoms

Analysis of the patient data resulted in a clear diagnosis in 1032 cases, but a detailed documentation of symptoms was only provided in 942 cases. Based on the descriptions of the symptoms of these cases, the most frequent primary efflorescences detected in patients with rosacea or POD were papules, persistent erythemata, telangiectasias and pustules; these were respectively observed in 64.8 % (n = 610/942), 56.2 %, 39.1 % and 30.5 % of patients, and occurred in various combinations (Figure 1). Furthermore, 689 patients (73.1 %) also reported a variety of other symptoms with the most prominent being pruritus (19.6 %, n = 135/689), closely followed by erythematous plaques (18.7 %) and desquamation (16.0 %). Ocular involvement and rhinophyma were identified in only 10.0 % and 9.3 % of cases, respectively (Figure 2). The ocular manifestation of rosacea was mainly detected in the form of conjunctivitis or blepharitis

Phenotypes

We were able to accurately evaluate the phenotypes of 975 patients (94.5 %) out of a total of 1032 that were included. We found that erythematotelangiectatic rosacea (ETR) (72.7 %, n = 709/975) and papulopustular rosacea (PPR) (72.4 %) did not differ significantly from each other when compared by the frequencies of their appearances (cumulated). However, if the phenotype were to be determined by the severest symptom, PPR (68.4 %) would clearly be the leading symptom,
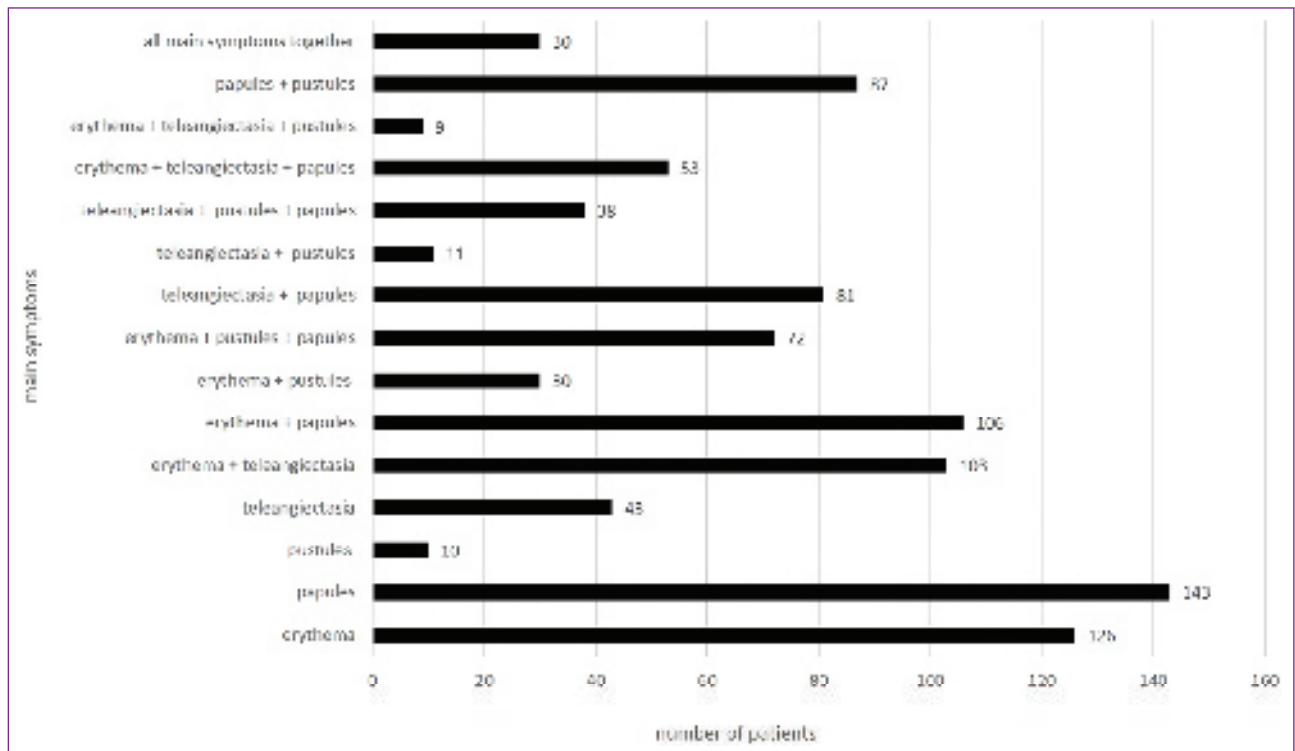
Figure 1 Distribution of the main symptoms of rosacea. This shows the frequency of the main facial symptoms or the various combinations with which the patients presented in our dermatologic outpatient clinic.
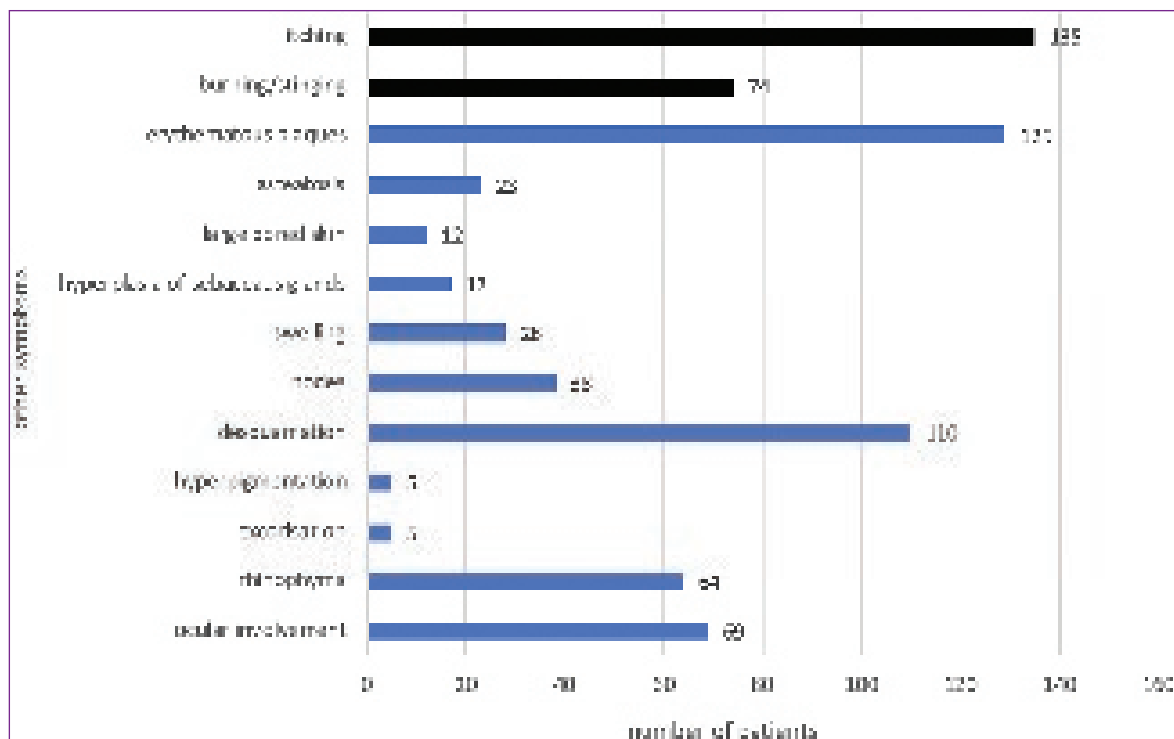

Figure 2 Distribution of patient-reported symptoms (black horizontal bars) and all other symptoms (blue horizontal bars). It shows all other symptoms that were documented in the patients' first consultations in our dermatology outpatient clinic.
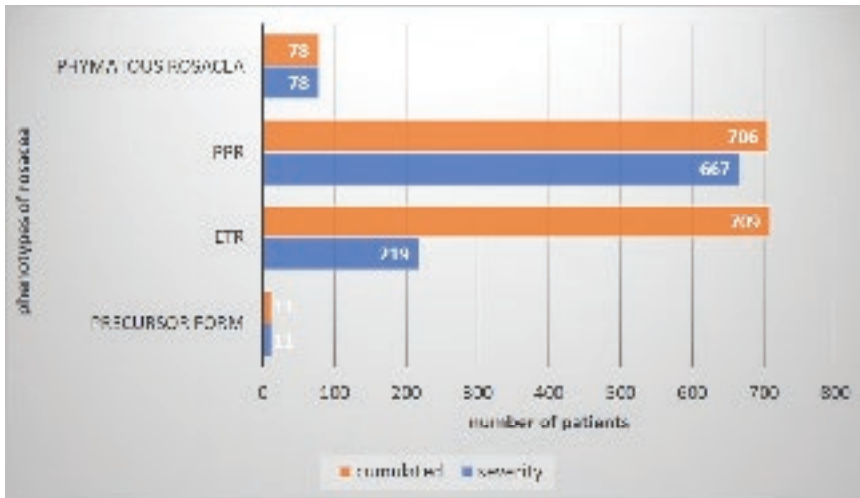
Figure 3 Distribution of the phenotypes of rosacea based on a cumulated-oriented and a severity-oriented determination of symptoms.

followed by ETR (22.5 %) and phymatous rosacea (8.0 %). Rosacea diathesis (transient erythema) was detected in only 1.1 % of all patients (Figure 3).

The most frequently observed phenotype combination was that between PPR and ETR (45.3 %) (Figure 4).

Special forms

Out of 1032 patients, 1000 (96.9 %) were further analyzed regarding the special forms of rosacea. Of this patient cohort, 158 (15.8 %) were diagnosed with special forms of rosacea.
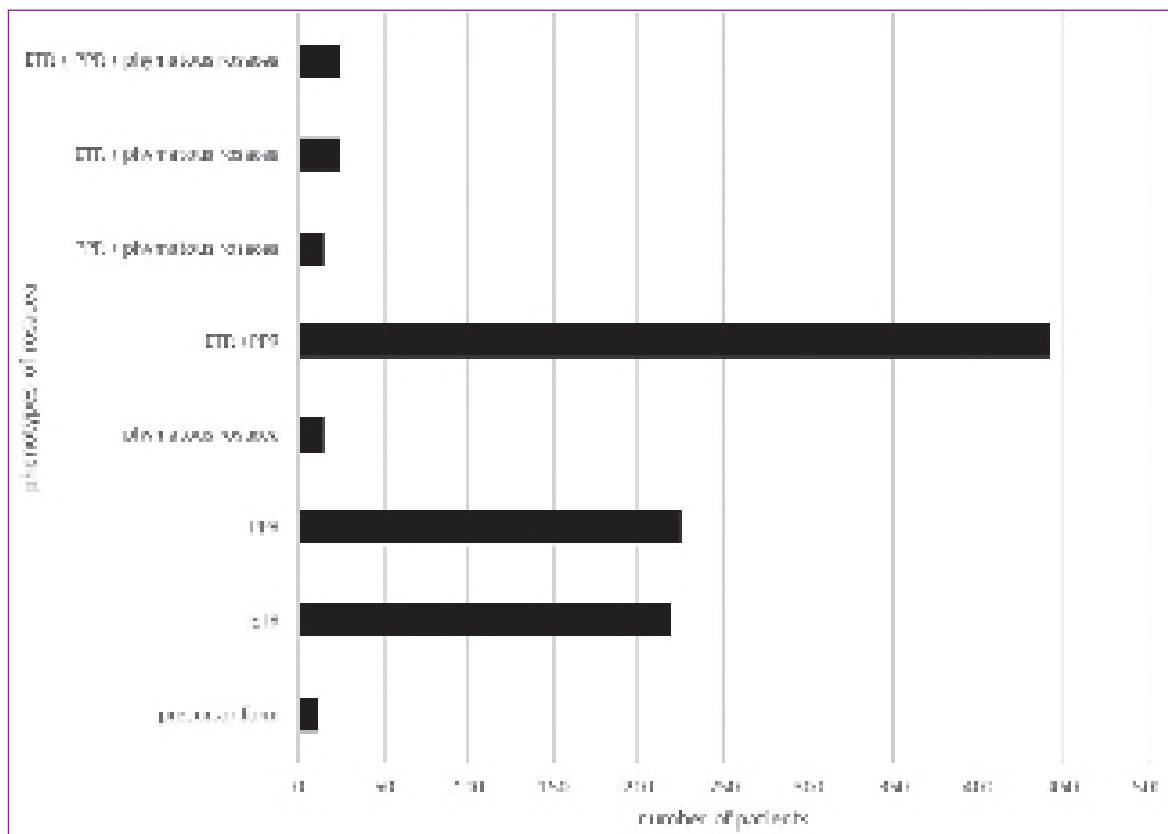

Figure 4 Individual and combined occurrence of different phenotypes in the clinical presentation of the patients.
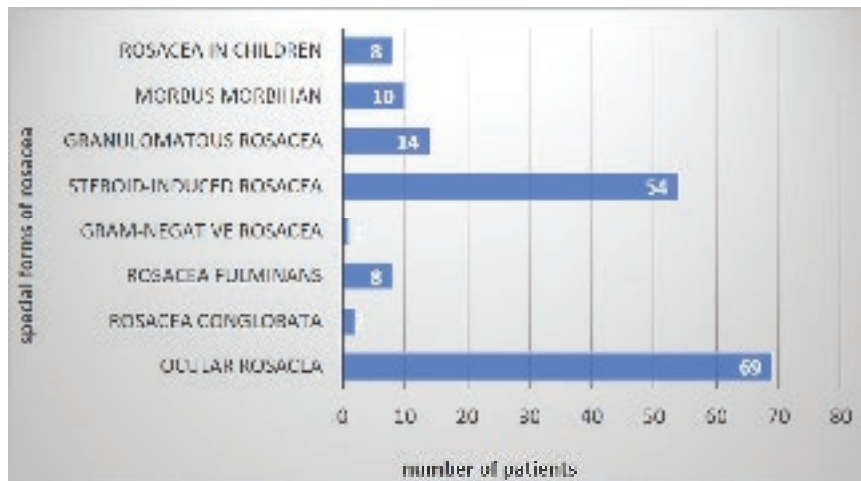
Figure 5 Distribution of the special forms of rosacea. The discrepancy between the total number of patients (158) diagnosed with special forms and the total number displayed on the Figure (166) is due to the sporadic occurrence of two distinct special forms in the same individual.

They occurred alone, in combination with the classic form and in a few cases two special forms occurred together in the same patient. Ocular rosacea, described in the medical notes as ocular involvement with symptoms such as blepharitis, conjunctivitis, dry and/or burning eyes, showed the highest prevalence in this category with 6.9 %, followed by steroid-induced rosacea with 5.4 % of the evaluated patients. Other special forms such as granulomatous rosacea, pediatric rosacea and rosacea fulminans were diagnosed at a very low rate of less than 1.0 % each (Figure 5). Morbihan disease/persistent edema was clinically diagnosed in 10 cases (1.0 %), of which only two were confirmed (by histological exclusion of several differential diagnoses) as Morbihan disease.

Therapy

Overall, 899 out of 1032 patients (87.1 %) received thorough therapeutic recommendations during the first visit. Topical medication as a monotherapy was the leading method of management in 66.3 % of these patients. In contrast, systemic

agents alone were prescribed in less than 6 % of the cases, making it the least recommended form of therapy after the combination of topical and systemic treatments (28.0 %) (Table 2). Regarding specific medications, 0.75 % metronidazole (gel, cream) and 40 mg modified release doxycycline preparation were by far the most frequently prescribed substances used in topical and systemic therapy, respectively (Table S1; online Supporting Information).

Discussion

Prevalence, gender and age

The prevalence of 1.4 % for patients with rosacea ($n_{rosacea}/n_{total}$ = 841/60965) in the outpatient clinic of the LMU is similar to that found in other studies in outpatient clinics, such as that of Doe et al. (1.8 %) and Gutierrez et al. (2.0 %) [13, 14]. However, there is a large variation in the general population, ranging from below 1.0 % [15] to above 20.0 % [16]. Latest surveys reported a prevalence of 12.3 % in Germany and 5.0 % in Russia in a prospective study [17]. This seems to be more accurate for the general population, since previously mentioned studies with very high or low results often had limitations such as special cohorts or different diagnostic criteria [15, 16]. The prevalence of patients with rosacea seen in dermatology practices may be considerably higher than the prevalence of these patients in outpatient dermatology clinics of university hospitals, because severe or complex cases are usually referred to university hospitals. Hence, our data sample from patients of the LMU outpatient clinic might represent a special cohort.

Patients' gender was predominantly female (69.3 %, n = 715/1032). Rueda et al. (76.0 %) and Khaled et al. (71.0 %) report similar results in clinical settings [18, 19]. Contrast studies of the general population report a more equal gender distribution [20–22], while in some other studies an even

Table 2 Frequency distribution of the total patient count, POD and rosacea by type of treatment received during the first visit.

	POD + Rosacea n (%)	POD n (%)	Rosacea n (%)
Topical treatment	596 (66.3)	133 (91.7)	463 (61.4)
Systemic treatment	51 (5.7)	1 (0.7)	50 (6.6)
Topical + systemic treatment	252 (28.0)	11 (7.6)	241 (32.0)
Total	899 (100)	145 (100)	754 (100)

greater male percentage has been reported among patients [21–23]. Therefore, gender might presumably be equally distributed in the general population.

Rosacea can be considered as a disease of adulthood with nearly 80.0 % of patients receiving their diagnosis after the age of 30, based on a large observational study from the UK [24]. Other studies conducted in large outpatient clinics in countries outside Europe reported similar results (mean age 49.0 years) [18, 19]. This is also consistent with the results of our study group (mean age 49.3 years). When stratified by gender, we found that women's age (48.5 years) was less than men's (50.9 years) at the time of the diagnosis. This is in line with a report of Schaefer et al., which found that women with rosacea were on average two years younger than men among the general population in Germany [21]. One reason for this could be an earlier diagnosis of women due either to an earlier onset or to earlier consultations with the doctor.

Interestingly, at the time of the diagnosis patients with POD were on average 10 years younger (38.7 years) than patients with rosacea, which is in accordance with the reports by Malik et al. (35.7 years, 1–74 years) and Hogan et al. (31.6 years, 1–74 years) [25, 26]. In contrast, phymatous rosacea was diagnosed at an average of 60.3 years, which is consistent with reviews from other studies [27]. Therefore, POD might occur more often in younger patients, while phymatous rosacea could occur in older ones.

In our study, patients with ocular rosacea received their diagnosis at the age of 54.0 years, which is consistent with the results of Akpek et al. and Lazaridou et al. [28, 29]. However, other special forms appeared earlier than the overall mean age of 49.3 years, including pediatric rosacea (mean age 6.4 years) and rosacea fulminans (mean age 48.4 years). Thorough studies about special forms are rare, but reviews of patients with rosacea fulminans report a rather young average age of onset of 31.3 years [30].

Symptoms

Regarding combinations of symptoms, that of erythema and papules occurred most frequently (11.3 %, n = 106/942), followed by erythema and telangiectasia (10.9 %). Our results tend to support the proposal of a symptom-oriented therapy because these primary efflorescences often occurred in various combinations [9].

Accumulated analysis showed papules (67.9 %) as the most frequent symptom, closely followed by erythema (64.2 %). Other studies from dermatological clinics showed erythema as the most frequent symptom, followed by papules and pustules [19, 31], while in the general population papules and pustules were less frequently seen [16, 17]. Overall, erythema is probably the most frequent symptom of rosacea, whereas in clinical settings it may result in a higher

percentage of papules since it could be the higher grades of rosacea that prompt patients to visit the doctor.

Rhinophyma was diagnosed in 64 patients (9.3 %). Rueda et al. (4.8 %) and Khaled et al. (3.7 %) reported roughly half the prevalence that we determined in our outpatient clinic [18, 19]. One reason for this could be the lighter skin type of the population in Germany compared to the darker skin types of the populations in Colombia and Tunisia, which are reported to be less affected by rosacea [1, 2]. In conclusion, phymatous changes are rare but have a higher prevalence in a clinical setting.

Phenotypes

Depending on the interpretation of the classification, multiple versions of analysis and different results would be possible. Our cumulated analysis showed ETR (72.7 %) as the most frequent form, closely followed by PPR (72.4 %). Regarding the most severe symptom of the phenotypes, PPR was diagnosed more often (68.4 %) than ETR (22.5 %). PPR was the most frequent form in studies from other dermatological clinics [18, 19]. Only Kyriakis et al. reported a higher prevalence for ETR (72.0 %) than for PPR (27.9 %) in a hospital-based outpatient setting [20].

The most frequent phenotype in females was PPR (73.5 %, n = 490/667). However, this was influenced by the fact that PPR was the dominating lesion in POD too. In contrast, phymatous rosacea occurred more often in men (71.8 %, n = 56/78); this has also been reported in other studies [19, 20, 27].

PPR was clearly the dominating phenotype in our outpatient hospital setting. Rosacea diathesis (transient erythema) and ETR are more often reported in the general population, whereas phymatous rosacea is rare, but more likely to be seen in the outpatient hospital setting than in the general population. A better international classification is required to avoid confusion in the interpretation of the phenotypes of rosacea, given the fact that rosacea patients often present with a wide range of symptoms that can occur in different combinations and variations. This has been previously recommended and discussed in several studies [7, 9].

Special forms

Special forms of rosacea were diagnosed in 15.8 % (n = 158/1000) of the analyzed patients. Data concerning the prevalence of special forms are scarce and there is no knowledge about their exact distribution.

Ocular rosacea was documented as the final diagnosis in 6.9 % of the analyzed patients. Here, we considered only patients with mild symptoms of ocular involvement such as blepharitis and dry eye, based on the S1 Guideline provided

by the German Society of Dermatology [12]. However, ocular involvement is estimated to occur in 20 % of patients with cutaneous rosacea [9]. Differences in physical examination, questionnaires, and in definitions of ophthalmic rosacea can often make differentiation difficult. Thus, it is important to screen patients thoroughly for ocular symptoms, and also consider some of the most relevant differential diagnoses, such as bacterial, viral, or allergic conjunctivitis, phlyctenular conjunctivitis or trauma, since they can be frequently overlooked [9].

We did not see steroid rosacea as often as reported by Khaled et al. (11.5 %) [19], which was slightly more than twice our result for this special form. Steroid-induced rosacea-like dermatitis (RD) has also been reported by other studies, such as Rathi et al., who described the clinical presentations of 110 cases collected over a two-year period [32], and Teraki et al., who attributed 22 of the 44 RD (50 %) cases diagnosed between 2005 and 2010 solely to topical steroid application [33]. Steroid rosacea is probably the second most frequent special form. It is therefore advisable to search for signs of steroid use.

Rosacea fulminans was diagnosed in eight cases. A great majority of these cases were women (6 cases, 75 %), which is in accordance with a recent literature review of cases from 1916 to 2016 (123 cases, 91 %). Furthermore, pregnancy has been increasingly associated with this form of rosacea [30]. Interestingly, in our study we found that 50 % of the women diagnosed with rosacea fulminans were either pregnant or breastfeeding.

The rarest forms seen in the outpatient clinic of the LMU were Morbihan disease, rosacea conglobata and gram-negative rosacea. Several case studies of these forms have been reported in the literature, but they often have a very low number of patients. An example is a case study from the University of Mainz, which reported only five cases of Morbihan disease admitted between 2008 and 2010 [34]. Thus, these forms are probably less frequent.

Therapy

The lack of a single therapeutic modality leading to a cure of rosacea has shifted the main focus of treatment to general measures and symptom control of the disease [35]. In our study, we found that a great majority of patients (94.3 %) were prescribed topical medication as monotherapy or in combination with systemic agents. This could be explained by the fact that topical treatment, alone or as part of a combination regime, has proven to be adequate in most patients with ETR or PPR [36], which, according to our results, were also the most frequent phenotypes. Moreover, due to the high recurrence rate as a chronic inflammatory skin disease, topical maintenance therapy is further recommended for long-term improvement [35].

Limitations

This study has some limitations, including its single-center format. While the Dermatology Department of the LMU is among the largest in Europe, our chosen cohort still cannot accurately represent the overall epidemiology of rosacea or POD. Retrospective analysis of data is another limitation since it is disadvantageous for assessment of rare diseases, as can be seen in our case with the special forms of rosacea, such as the gram-negative form, rosacea conglobata, or rosacea fulminans. Furthermore, the majority of cases were documented as free texts, which allows for a certain margin of error during retrospective assessment. Lastly, it should also be mentioned that this study was conducted nearly six years ago, which, depending on new medical and social developments, could be a potential weakness in our conclusions.

The period of three years and the large number of rosacea patients studied, provided the opportunity to estimate an approximate frequency of rosacea forms and POD in a hospital-based outpatient care setting in Germany. Special forms are rare and make it harder for the clinician to make a specific diagnosis. However, it is important to be aware of these forms in unusual cases or cases of escalating rosacea, because treatment success may depend on it.

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