

Malignant and benign forms of atrophic papulosis (Köhlmeier–Degos disease): systemic involvement determines the prognosis

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Summary

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Conflicts of interest

None declared.

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Background Atrophic papulosis (Köhlmeier–Degos disease) is a rare disease of unknown aetiology. The cutaneous signs – papular skin lesions with central porcelain-white atrophy and surrounding telangiectatic rim – are almost pathognomonic. Extracutaneous, systemic involvement includes multiple limited infarcts of the gastrointestinal system, central nervous system and other organs.

Objectives To assess prospectively the demographics, epidemiological data and prognosis of patients with atrophic papulosis evaluated in a single centre.

Methods A prospective, single-centre, cohort study at diagnosis was performed on a series of 39 patients with atrophic papulosis, first seen between 2000 and 2007 and evaluated up to 2012.

Results The occurrence of cutaneous lesions defined the onset of disease in all cases. The mean age of onset was 35.4 ± 12.3 years and the male-to-female ratio was 1 : 1.4. In total, 9% of patients reported familial occurrence. Extracutaneous (systemic) signs were recorded in 29% of the patients, whereas the median time for development of systemic manifestations was 1 year (0.03–0.97 quantiles: 0–7 years) after the occurrence of cutaneous lesions. The prognosis was determined mainly by the presence of systemic involvement. 73% of the patients with systemic manifestations (73% developed intestinal perforation) died, while none of the patients with only cutaneous disease had a lethal outcome. The cumulative 5-year survival rate in patients with systemic disease was 54.5%.

Conclusions Atrophic papulosis, previously called malignant atrophic papulosis, should be classified into a malignant, systemic form and a benign, cutaneous one, the latter being more common. The probability of having a benign form of the disease at onset is approximately 70%, increasing to 97% after 7 years of monosymptomatic cutaneous course.

What's already known about this topic?

- Existing information on atrophic papulosis comes mostly from case reports, and there has been no prospective study of the disease.

What does this study add?

- The first data on the demographics, epidemiology and prognosis of atrophic papulosis are provided through a prospective cohort study.
- The previously so-called 'malignant atrophic papulosis' (MAP) should be renamed 'atrophic papulosis' and classified into a malignant, systemic form (MAP) with

severe prognosis and a more common, benign, cutaneous form (benign atrophic papulosis, BAP).

- The probability of a benign course increases with the duration of BAP, and reaches 97% at 7 years.

Atrophic papulosis (Köhlmeier–Degos disease or Degos disease), previously also called malignant atrophic papulosis, is a rare disorder¹ that was described first by Köhlmeier² and documented as a separate entity by Degos *et al.*³ Currently fewer than 200 cases have been described in the literature.

The first manifestation of the disease usually occurs between the 20th and 50th year of life.^{4,5} However, single cases of atrophic papulosis in newborns have also been described.⁶ A genetic predisposition has been suggested, as there have been reports of clusters of patients among members of the same family. Within these families, first-degree relatives were more frequently affected, and therefore an autosomal dominant trait was considered to be the most probable mode of inheritance.^{7–9}

Atrophic papulosis is diagnosed through pathognomonic skin lesions: centrally porcelain-white atrophic papules with an erythematous, telangiectatic rim (Fig. 1). Typically, the lesions are about 0.5–1 cm in diameter and appear initially as small erythematous papules, mainly on the trunk and upper extremities. The scalp and face seem to stay remarkably free of lesions. A sole cutaneous involvement has been reported in 37% of case reports,¹⁰ and a single small case series has also previously been presented.¹¹ Extracutaneous (systemic) involvement can occur simultaneously with the skin lesions or later, and multiple infarctions on the gastrointestinal system, central nervous system (CNS) and other organs have also been described.⁵ Bowel perforation, thrombosis of the cerebral arteries or massive intracerebral haemorrhage are major clinical signs leading to a severe prognosis, while no specific laboratory parameters have been reported.¹² The aetiology of the



Fig 1. Skin lesions on the lower arm of a 63-year-old woman with atrophic papulosis. Characteristic lesions with porcelain-white atrophic centre and a surrounding erythematous rim.

disease remains unknown, but coagulopathy, vasculitis and primary dysfunction of endothelial cells have been suggested.¹

In contrast to the systemic form of the disease, which can exhibit a severe course, the existence of a benign monosymptomatic cutaneous form has been suggested by several authors.¹³ Many of these cases show signs of inheritance, especially between first-degree relatives.^{8–10} However, these two forms have not been unambiguously distinguished from each other. The fact that systemic involvement can develop suddenly, after many years of symptoms solely on the skin, indicates the need for data to make this classification possible.

In the present prospective cohort study we provide for the first time, to our knowledge, case series data from a single centre, as well as data allowing stratification of the patients into two groups with diversified prognostic forms of the disease.

Patients and methods

Collection of data

Demographic and clinical data were collected in a prospective, single-centre, cohort study at diagnosis from a series of 39 patients with atrophic papulosis, first seen between 2000 and 2007, and followed until 2012 (Table 1). The cases were referred from various centres all over the world to the evaluation centre in Berlin and later in Dessau, Germany. All patients had received a skin biopsy, and the evaluation was used to support the clinical picture in confirming the diagnosis by at least one dermatology expert. General blood examinations and a faecal occult blood test were performed in all patients. Further diagnostic procedures, such as brain magnetic resonance imaging, colonoscopy and gastroscopy, were performed with any report of specific or nonspecific symptomatology on the central or peripheral nervous system, the gastrointestinal tract or any other organ system. In the case of a positive result the patient was assigned to the group with systemic involvement. Only patients without extracutaneous (systemic) involvement during the entire follow-up period were classified as having monosymptomatic cutaneous disease.

Additional clinical data were obtained with the help of a standard questionnaire, which can be obtained from the website of the international patients' self-aid group on Degos disease (www.degosdisease.com). The role of this group was to function as a link between the patients and the experts on the disease. All cases have been followed up prospectively, the end point of the follow-up being defined as the time point of

Table 1 Demographic and clinical data of 39 patients with (malignant) atrophic papulosis

	All patients	MAP	BAP	Significance
Number	39	11/38	27/38	
Male	16	4/15	11/15	NS
Female	23	7	16	
Age of onset (years), mean \pm SD; median (min–max)				
Overall	35.4 \pm 12.3; 36.5 (5–60)	35.5 \pm 13.6; 38 (5–56)	35.8 \pm 11.8; 33 (13–60)	NS
Male	31.8 \pm 11.4; 33 (5–48)	30 \pm 18.2; 37 (5–48)	32.4 \pm 9.1; 33 (13–44)	NS
Female	38.0 \pm 12.4; 40 (19–60)	37.5 \pm 10.7; 39 (19–56)	38.3 \pm 12.9; 36 (19–60)	
Familial occurrence	3/34	1	2	NS
Mean time for the development of systemic signs (n = 9)		1 year (Q _{0.03–0.97} : 0–7 years)		
Mortality	8/38	8/11	0/27	P < 0.05
Mean survival time from the development of systemic disease (n = 9)		0.9 years (Q _{0.03} : 0 years)		

MAP, malignant atrophic papulosis (patients with systemic manifestations); BAP, benign atrophic papulosis (patients with cutaneous signs only); Q, quantile.

the last questionnaire submission, with questionnaires included until the end of 2012.

Statistical analysis

Statistical significance was calculated by the two-sample independent-groups t-test. The statistical significance of the cross tabulations was evaluated using Kendall's tau coefficient and Spearman's rank correlation coefficient. Estimation of the survival rate was performed using Kaplan–Meier survival analysis. Statistical significance was considered with P-values < 0.05. The statistical analysis and graphs were produced with SPSS version 19 (IBM Corporation, Armonk, NY, U.S.A.).

Results

Sex distribution and age of manifestation

Of the 39 recruited patients, 16 were male and 23 were female, a male-to-female ratio of 1 : 1.4 (Table 1). The average age at disease onset in male patients was 31.8 \pm 11.4 years [95% confidence interval (CI) 25.7–37.8] and in female patients 38.0 \pm 12.4 years (95% CI 32.6–43.8; P > 0.05). The overall mean age of onset was 35.4 \pm 12.3 years (95% CI 31.5–39.4) (Fig. 2).

Family history and systemic involvement

In 11/38 patients (29%) available for analysis (one male patient was lost to follow-up), systemic disease was diagnosed, whereas 27/38 patients (71%) presented only cutaneous signs throughout the follow-up period. More specifically, 27% of male patients (four of 15) and 30% of female patients (seven of 23) developed signs of systemic disease (P > 0.05). In addition, the possibility of occurrence

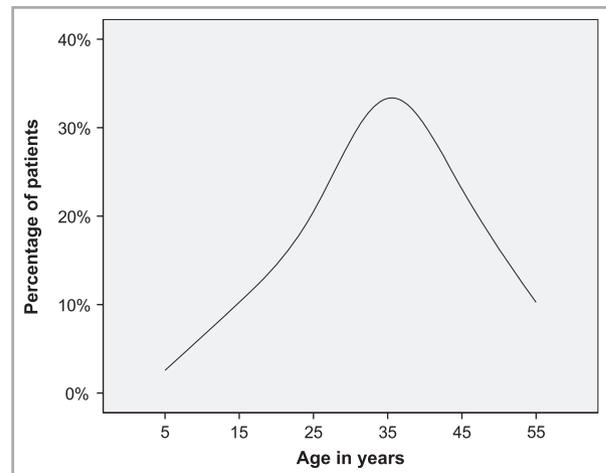


Fig 2. Distribution of the age of onset (mean 35.4 \pm 12.3 years, 95% confidence interval 31.5–39.4).

of familial atrophic papulosis was examined (data available for 34 patients). Three of the 34 patients (9%) confirmed and 31 patients (91%) denied the occurrence of the disease in anyone else in their family. In the former group, one of the three patients (33%) and in the latter group eight of the 31 patients (26%) developed systemic disease (P > 0.05).

Disease duration until systemic involvement

In patients with extracutaneous involvement, a first systemic manifestation followed a median of 1 year (0.03–0.97 quantiles: 0–7 years) after disease onset (Fig. 3). Thus, in 97% of the patients with systemic disease, organ involvement began within the first 7 years of the disease. The gastrointestinal tract and CNS were involved in eight of 11 (73%) and

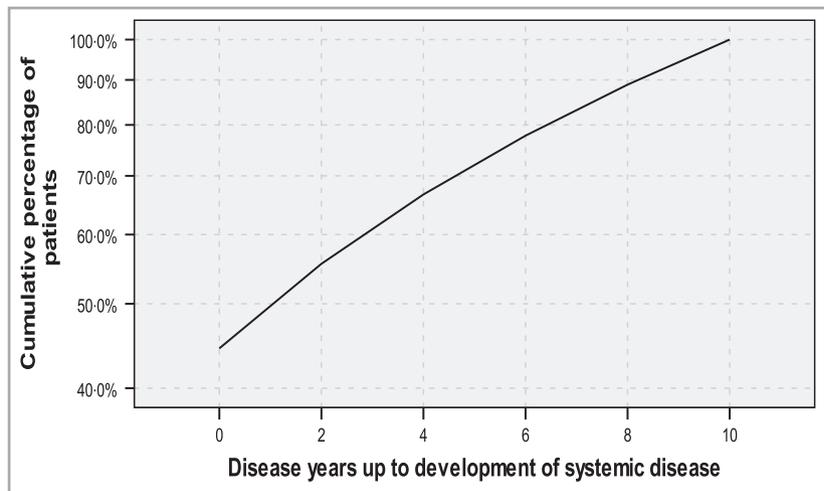


Fig 3. Time interval between diagnosis and development of systemic disease in patients with systemic involvement (median 1 year; 0.03–0.97 quantiles: 0–7 years).

seven of 11 patients (64%) with systemic involvement, respectively. Bleeding from the upper or lower gastrointestinal tract and/or nonspecific symptoms, such as tingling and numbness or abdominal pain, and CNS signs, such as paresis and paralysis, were recorded. Five of the 11 patients (45%) had involvement of other internal organs, such as the heart, eyes and lungs, while seven of the 11 patients (64%) had simultaneous disease of multiple organ systems (Table 2).

Mortality and systemic vs. only cutaneous involvement

The overall mortality was 21% [eight of 38 patients with follow-up: three male (20%) and five female (22%); $P > 0.05$], all of them having systemic involvement. In systemic disease the mortality rate was 73% (eight of 11 patients). The cumulative 5-year survival rate in this latter group was 54.5% (standard error 1.71, 95% CI 2.6–9.4). The mean survival time from the development of systemic disease was 0.9 years (0.03 quantile: 0 years; $n = 9$). No lethal cases were observed

Table 2 Demographic data of patients with malignant atrophic papulosis from the current and previous studies

	Current study Prospective, monocentric	Assier <i>et al.</i> ¹¹ Prospective, multicentric	Burg <i>et al.</i> ¹⁰ Literature review
Number of patients	39	15	106
Male/female (ratio)	16/23 (1 : 1.4)	6/9 (1 : 1.5)	63/43 (1.47 : 1)
Age at onset (years), median (min–max)	36.5 (5–60)	34.0 (13–68) ^a	35.0 ^a
Patients with systemic manifestations, n (%)	11/38 (29)	9/15 (60)	67/106 (63.2)
Multiorgan involvement, n (%)	7/11 (64)	5/9 (56)	33/67 (49)
Organs involved, n (%)			
GI tract	8/11 (73)	9/9 (100)	51/67 (76)
CNS	7/11 (64)	2/9 (22)	20/67 (30)
Lung	1/11 (9)	2/9 (22)	16/67 (24)
Eye	2/11 (18)	4/9 (44)	14/67 (21)
Heart	2/11 (18)	2/9 (22)	NR
Kidney	0/11 (0)	1/9 (11)	NR
Patients with cutaneous lesions only, n (%)	27/38 (71)	6/15 (40)	39/106 (36.8)
Mortality, n (%)			
Total	8/38 (21)	NR	51/106 (48.1)
Male	3/15 (20)	NR	36/63 (57)
Female	5/23 (22)	NR	15/43 (35)
Patients with systemic disease	8/11 (73)	NR	50/67 (75)
Patients with skin lesions only	0/27 (0)	NR	1/39 (3)
Mean survival time from development of systemic disease	0.9 years	NR	< 5 years
Familial occurrence, n (%)	3/34 (9)	NR	12/64 (19)
Systemic manifestation in familial disease	1/3 (33)	NR	1/12 (8)
Systemic manifestation in spontaneous disease	8/31 (26)	NR	45/52 (87)

GI, gastrointestinal; CNS, central nervous system; NR, not reported. ^aAge at diagnosis.

Table 3 Follow-up plan for patients with atrophic papulosis

Diagnosis and follow-up in specialized centres
Essential diagnostic tools
Whole-skin examination
Skin biopsy for histological examination
Faecal occult blood test
Ocular fundus examination
Additional if organ symptomatology suspected
Colonoscopy/gastrosocopy/laparoscopy
Brain magnetic resonance imaging with contrast
Heart ultrasonography
Thorax computed tomography with contrast
Kidney function test (clearance)
Follow-up
Twice yearly, 0–7 years
Once yearly, 7–10 years
Follow-up with the essential diagnostic tools except skin biopsy, and, if symptoms, additional examinations as above

among the 27 patients with only cutaneous involvement ($P < 0.05$).

Discussion

This prospective cases series with demographic and epidemiological analysis of 39 patients with atrophic papulosis provides important data about the classification of the disease and its prognosis. The disease occurred generally in the fourth decade of life, and there was a trend of earlier onset in male patients. In all patients the sign of onset was the characteristic cutaneous lesions.

The prognosis of the disease was severe, with an overall mortality of 21%. Approximately 30% of these patients developed systemic manifestations, and three-quarters of them died due to systemic complications (bowel perforation, CNS thrombotic lesions).¹⁰ Only 55% of the patients with systemic involvement survived at least 5 years. There was an early development of systemic manifestations, a median of 1 year after the onset of the disease with skin lesions. In addition, the majority of these patients (97%) developed systemic signs within the first 7 years of the disease course. The most common variants of systemic involvement were the gastrointestinal tract, in 73% of the patients with systemic disease, followed by the CNS (64%) and involvement of multiple organ systems (64%).^{10,11}

In contrast, no patient with only cutaneous lesions had a lethal outcome. The probability of a benign course increased with time, from 71% at onset to 97% after 7 years of monosymptomatic cutaneous disease. The markedly lower rates of 37–40% of patients having monosymptomatic cutaneous disease, compared with published case reports and a smaller case series, may indicate an overestimation of the overall severity of the disease.^{10,11}

Despite the slight female preponderance, there was no sex correlation with the systemic form of atrophic papulosis, and

no sex-associated prognosis, in contrast to the report by Burg *et al.*¹⁰ Furthermore, no prognostic difference was found for familial vs. spontaneous disease.

Overall, comparison of our data with those of the small multicentric series of 15 patients reported by Assier *et al.*¹¹ and the literature review by Burg *et al.*¹⁰ shows similarities in most demographic, epidemiological and clinical parameters (Table 2). Major differences were detected only in the proportions of patients with systemic involvement, sex-associated mortality and the rate of systemic involvement in spontaneous vs. familial cases.

In conclusion, atrophic papulosis is a rare disease with a severe and potentially life-threatening systemic form. In contrast, the cutaneous form is remarkably benign, a fact that confirms the findings of other authors^{10,13–15} and indicates that the previously so-called 'malignant atrophic papulosis' should be renamed 'atrophic papulosis' and classified into a malignant systemic disease (malignant atrophic papulosis) and a benign cutaneous disease (benign atrophic papulosis). Patients should be worked up and followed in specialized centres following a standard plan (Table 3). The probability of a benign course increases with the duration of benign atrophic papulosis, becoming 97% at 7 years. Finally, sex and a positive family history do not influence the long-term prognosis.

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