

ORIGINAL PAPER

Mucin is not a rare finding in rosacea

A. FERNANDEZ-FLORES

Service of Cellular Pathology, Clinica Ponferrada,
Ponferrada, Spain

Abstract

Mucin deposit is a feature that is not commonly mentioned in textbooks when talking about rosacea. Nevertheless, it is one of the prominent findings of a severe variant of the phymatous type of rosacea known as the fibrous type. We retrospectively investigated 20 cases of early stages of rosacea and examined the mucin deposit in them, with histochemical stains (Alcian Blue and Periodic Acid-Schiff). We found granulomas in 20% of these cases. Alcian Blue positive deposits of mucin were found in all cases with granulomas. The mucin was located in the granulomas (four cases) as well as in the infundibulum (one case). No deposits of mucin were evidenced in the dermis out of the granulomas, apart from the normal mucin of papillary and adventitial dermis. Periodic Acid-Schiff did not show any deposits in any case. Serologic lupus markers were negative in all patients with mucin deposits. We conclude that: (a) mucin is a common finding in granulomas of rosacea; (b) this mucin is probably not related to any progression to the mucinous variant of rhinophyma; (c) since discoid erythematosus lupus is a clinical differential of rosacea, it is important to be aware of the fact that mucin is a common finding in the granulomas, in order not to misdiagnose both entities.

Keywords: rosacea, rhinophyma, granulomatous rosacea, mucin, granuloma.

Introduction

Several morphologic changes are described in rosacea and granulomas are one of them. However, some features have only been described in advanced stages of rosacea, i.e. rhinophyma. That happens, for instance to mucin deposit. The latter has been observed in a certain type of rhinophyma, considered as a severe variant. In such a variant, large amounts of mucin in the stroma, as well as fibroplasias, are characteristic [1, 2].

Our claim was to investigate if early stages of rosacea are really devoid of mucin deposit, and if not, to see where such deposits could be found. For that, we designed a retrospective study of 20 cases of rosacea biopsied in early stages, investigating all of them with histochemical stains for mucin.

Material and Methods

We studied 20 biopsies diagnosed as rosacea from our archives. All biopsies were reviewed again, in order to confirm the diagnoses. In all cases, we performed histochemical stains of Alcian Blue and Periodic Acid-Schiff (PAS). In cases with granulomas, Ziehl-Neelsen was also performed.

Table 1 shows the Alcian Blue staining procedure that was used.

Table 1 – Alcian Blue histochemical staining performed

1. Sections were taken to water.
2. We stained with Alcian Blue solution pH 2.5 for 5 minutes.
3. We washed with water.
4. Counterstaining was done in 0.1% Nuclear Fast Red for 5 minutes.
5. We washed with water.
6. We dehydrated, cleared and mounted them.

Table 2 shows the Periodic Acid-Schiff staining procedure used. In cases in which mucin deposits were evidenced, we reviewed the clinical history of the patients.

Table 2 – Histochemical staining for Periodic Acid-Schiff that was performed

1. We brought sections to water.
2. We treated with 1% Periodic Acid for 10 minutes.
3. We washed with water.
4. We treated with Schiff's reagent for 10 minutes.
5. We washed well in tap water.
6. We stained nuclei with Carazzi's Hematoxylin for 2 minutes.
7. Differentiation was obtained using acid alcohol.
8. Blue in Scott's tap water.
9. We dehydrated, cleared and mounted them.

Results

Some details of the 20 patients are shown in Table 3, including gender and age.

Table 3 – Cases of rosacea that were studied

Case no.	Gender	Age [years]	Granulomas	Alcian Blue	PAS
1.	M	88	No	Negative	Negative
2.	M	32	No	Negative	Negative
3.	F	64	No	Negative	Negative
4.	F	20	No	Negative	Negative
5.	F	75	No	Negative	Negative
6.	M	71	No	Negative	Negative
7.	F	82	No	Negative	Negative
8.	F	33	No	Negative	Negative
9.	F	46	Yes	Positive (granulomas)	Negative
10.	F	35	No	Negative	Negative
11.	M	29	No	Negative	Negative

Case no.	Gender	Age [years]	Granulomas	Alcian Blue	PAS
12.	F	55	Yes	Positive (granulomas)	Negative
13.	M	50	Yes	Positive (granulomas)	Negative
14.	M	58	No	Negative	Negative
15.	F	64	No	Negative	Negative
16.	M	68	No	Negative	Negative
17.	F	39	No	Negative	Negative
18.	F	55	No	Negative	Negative

Case no.	Gender	Age [years]	Granulomas	Alcian Blue	PAS
19.	M	68	No	Negative	Negative
20.	M	63	Yes	Positive (granulomas & Negative infundibulum)	

Ages (years) ranged from 20 to 88 (mean 54.75-year-old). Granulomas were evidenced in 4/20 cases (20%). Alcian Blue positive deposits of mucin were found in 4/20 cases (20%) (Figure 1).

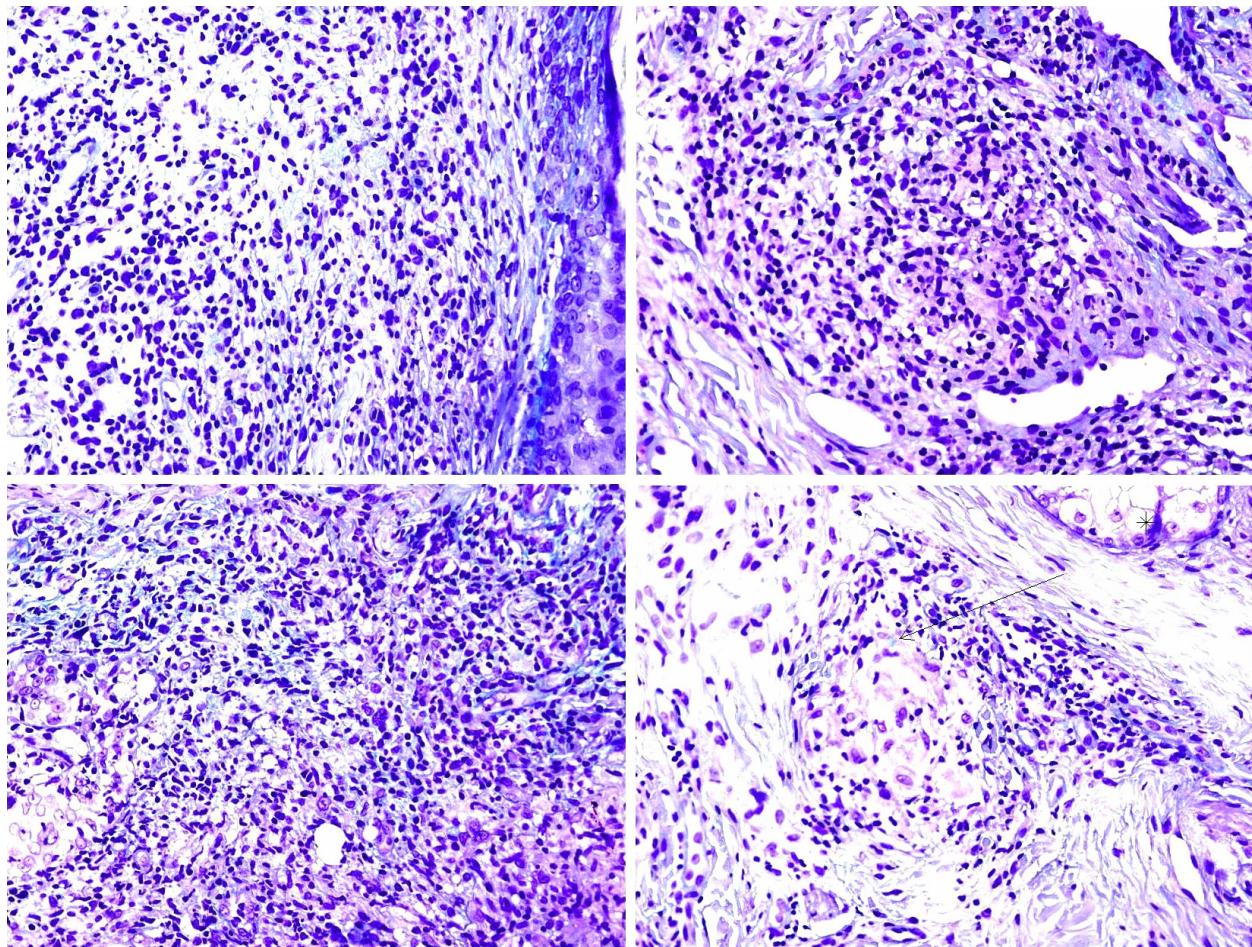


Figure 1 – Top left (case no. 20): close to the infundibulum (right) a granuloma with moderate amount of mucin, can be seen. Top right (case no. 9): mild deposits of mucin in the granulomas. Bottom left (case no. 13): moderate amounts of Alcian Blue positive deposits. Bottom right (case no. 12): in this case, only mild deposits of mucin were seen in the periphery of the granulomas (arrow). A sebaceous gland can be observed on the top.

The mucin deposits varied from mild (Figure 1, bottom right) to more abundant (Figure 1, top, left). In all cases with granulomas, Alcian Blue positive deposits were evidenced. The mucin was mainly located in the granulomas. One of the cases also showed mucin deposits in the infundibulum as well (case no. 20) (Figure 2).

No deposits of mucin were evidenced in the dermis out of the granulomas, apart from the normal mucin of papillary and adventitial dermis. Periodic Acid-Schiff did not show any deposits in any case. Ziehl-Neelsen did not demonstrate bacilli in any case.

None of the patients with mucin deposits had any symptoms of lupus erythematosus of any type, and no autoantibodies were found in the serum. Rheumatoid factor was negative in them.

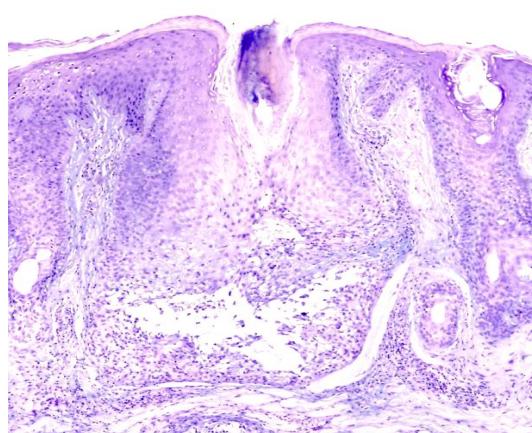


Figure 2 – Case no. 20: in this case, the mucin was also evidenced in the infundibulum.

When the clinical history of patients with granulomas was revised, all of them had had a good response to

medical treatment, and no evolution into rhinophyma had been seen (Table 4).

Table 4 – Follow up of the patients in whom mucin deposits were seen

Case no.	Gender	Age [years]	Follow up after the biopsy was performed [months]	Other accompanying diseases	Clinical evolution of the rosacea symptoms
01-0020	10. F	35	89	Hyperuricemia	Improvement under medical treatment.
05-4430	12. F	55	48	Fibromyalgia	Improvement under medical treatment.
99-6010	13. M	50	122	HIV+, since 12 years ago	Good response to medical treatment, with some relapses during these last few years.
08-3831	20. M	63	13	1. Prostatic hyperplasia; 2. Lipoma; 3. Two basal cell carcinomas; 4. Varices.	Persistence of some plaques in cheeks. Pruritus has nearly disappeared.

Discussion

Rhinophyma is considered as a late stage of rosacea [1], and it is included in the more generic phymatous subtype of the disease [3]. Obviously, rosacea does not always evolve into rhinophyma, mainly due to proper early treatment. Nevertheless, when rosacea is more advanced, treatment is not so effective in stopping the progression into rhinophyma [4]. Such progression is more common in men [5] and it is also more frequent in people of Celtic origin [6, 7].

However, not all types of rhinophyma are the same: a common variant and a severe variant are distinguished [2]. Intense dermal fibroplasia as well as large amounts of mucin in the stroma seems characteristic of the severe variant [1, 2]. Deposit of mucin is usually not described in early stages of rosacea in textbooks [8, 9], and that was also our experience in most of the examined cases. Nevertheless, 25% of our cases showed mucin related to the granulomatous reaction.

The led us to the question on whether granulomas with mucin might have prognostic implications in rosacea. In that respect, there is a variant of rosacea, called "granulomatous" [3, 10] due to the fact of the prominent granulomatous infiltrate in it. Most groups report how this variant responds well to the treatment that is usually applied in common rosacea [11–14]. Nevertheless, no description of mucin in such granulomatous infiltrate has previously been studied to the best of our knowledge, so the question on the prognosis of "granulomatous rosacea with mucin" is still unsolved.

The association of mucin and a granulomatous infiltrate is not unique in dermatopathology, and many other examples have been described. Probably the best known is granuloma annulare [15]. Also, a variant of scleromyxedema with a granulomatous pattern mimicking interstitial granuloma annulare has been described [16]. Interestingly, some have demonstrated that granulomatoses, such as granuloma annulare, are related to the abundance of heparan sulfate [18], a type of glycosaminoglycan that is most common on the surface of keratinocytes [19]. Furthermore, some have investigated the deposit of heparan sulfate in several inflammatory conditions of the skin and found important amounts of the substance *only* in disorders with a predominance of histiocytes in the inflammatory infiltrate [20]. In that respect, the pattern of histochemical staining that we saw in our cases is consistent with sulfomucins [21].

One of our cases showed mucin associated to the

disruption of the infundibulum, and this finding would be consistent with the hypothesis of the infundibulum or the granulomas as responsible for the mucin deposit. This contrasts with the hypothesized origin of the mucin in the severe variant of rhinophyma, where an origin from fibroblasts is suggested [2]. Some, for instance, have hypothesized that mucin deposit in rhinophyma could have a pathogenesis similar to elephantiasis, where the lymphatic stasis stimulates fibroblasts to produce deposits of collagen and glycosaminoglycans [2]. Nevertheless, the granulomatous infiltrate does not necessarily have to be the direct source of mucin: some have claimed that histiocytes could stimulate fibroblasts to shed mucin into the interstitium [20].

To give an answer to the question on if "mucinous granulomas" could have a role in the progression of the disease to the "mucinous" advanced stages of the disease, further studies would, obviously, need to be carried out. Nevertheless, some facts of our study seem contrary to such hypothesis. Firstly, all cases in which granulomas were seen had mucin. Secondly, 20% of cases had mucin; if all of these cases progressed into rhinophyma that would mean a high incidence of the mucinous variant of such disease, which is not the case. Thirdly, in patients in whom we had a long follow up of several years, progression to rhinophyma was not evidenced, in spite of the mucin deposit.

Conclusions

Therefore, we conclude that: (a) mucin is a common finding in granulomas of rosacea; (b) this mucin is probably not related to any progression to the mucinous variant of rhinophyma; (c) since discoid erythematous lupus is a clinical differential of rosacea, it is important to be aware of the fact that mucin is a common finding in granulomas, in order not to misdiagnose both entities.

References

- [1] TOPE WD, SANGUEZA OP, *Rhinophyma's fibrous variant. Histopathology and immunohistochemistry*, Am J Dermatopathol, 1994, 16(3):307–310.
- [2] ALOI F, TOMASINI C, SORO E, PIPPIONE M, *The clinicopathologic spectrum of rhinophyma*, J Am Acad Dermatol, 2000, 42(3):468–472.
- [3] WILKIN J, DAHL M, DETMAR M, DRAKE L, LIANG MH, ODOM R, POWELL F; NATIONAL ROSACEA SOCIETY EXPERT COMMITTEE, *Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea*, J Am Acad Dermatol, 2004, 50(6):907–912.

- [4] BERG M, LIDÉN S, *An epidemiological study of Rosacea*, Acta Derm Venereol, 1989, 69(5):419–423.
- [5] BUECHNER SA, *Rosacea: an update*, Dermatology, 2005, 210(2):100–108.
- [6] CEILLEY RI, *Advances in the topical treatment of acne and rosacea*, J Drugs Dermatol, 2004, 3(5 Suppl):S12–S22.
- [7] GUPTA AK, CHAUDHRY MM, *Rosacea and its management: an overview*, J Eur Acad Dermatol Venereol, 2005, 19(3):273–285.
- [8] IOFFREDA MD, Inflammatory diseases of hair follicles, sweat glands, and cartilage, In: ELDER DE (ed), *Lever's histopathology of the skin*, Lippincott Williams and Wilkins, Philadelphia, 2005, 469–512.
- [9] MCKEE PH, CALONJE E, GRANTER SR, *Rosacea*. In: MCKEE PH, CALONJE E, GRANTER SR (eds), *Pathology of the skin with clinical correlations*, Elsevier Mosby, Philadelphia, 2005, 1121–1124.
- [10] SÁNCHEZ JL, BERLINGERI-RAMOS AC, DUEÑO DV, *Granulomatous rosacea*, Am J Dermatopathol, 2008, 30(1):6–9.
- [11] HELM K, MENZ J, GIBSON L, DICKEN CH, *A clinical and histopathologic study of granulomatous rosacea*, J Am Acad Dermatol, 1991, 25(6 Pt 1):1038–1043.
- [12] DROLET B, PALLER AS, *Childhood rosacea*, Pediatr Dermatol, 1992, 9(1):22–26.
- [13] KHOKHAR O, KHACHEMOUNE A, *A case of granulomatous rosacea: sorting granulomatous rosacea from other granulomatous diseases that affect the face*, Dermatol Online J, 2004, 10(1):6.
- [14] DA COSTA JB, COUTINHO VS, DE ALMEIDA LS, GOMES MM, *Granulomatous rosacea in infants. Report of three cases and discussion of the differential diagnosis*, Dermatol Online J, 2008, 14(2):22.
- [15] DABSKI K, WINKELMANN RK, *Generalized granuloma annulare: histopathology and immunopathology. Systematic review of 100 cases and comparison with localized granuloma annulare*, J Am Acad Dermatol, 1989, 20(1):28–39.
- [16] STETSENKO GY, VARY JC JR, OLERUD JE, ARGENTI ZB, *Unusual granulomatous variant of scleromyxedema*, J Am Acad Dermatol, 2008, 59(2):346–349.
- [17] RONGIOLETTI F, COZZANI E, PARODI A, *Scleromyxedema with an interstitial granulomatous-like pattern: a rare histologic variant mimicking granuloma annulare*, J Cutan Pathol, 2009 Jul 22 [Epub ahead of print].
- [18] BANDEL C, DEPRISCO G, COCKERELL CJ, EHRIG T, *Abundance of interstitial heparan sulfate in granuloma annulare but not in other mucinous skin diseases*, J Cutan Pathol, 2002, 29(9):524–528.
- [19] DAVID G, BAI XM, VAN DER SCHUEREN B, CASSIMAN JJ, VAN DEN BERGHE H, *Developmental changes in heparan sulfate expression: in situ detection with mAbs*, J Cell Biol, 1992, 119(4):961–975.
- [20] DEPRISCO G, BANDEL C, COCKERELL CJ, EHRIG T, *Interstitial heparan sulfate in granulomatous inflammatory skin diseases*, J Am Acad Dermatol, 2004, 50(2):253–257.
- [21] SPICER SS, *Diamine methods for differentiating muco-substances histochemically*, J Histochem Cytochem, 1965, 13:211–234.

Corresponding author

Angel Fernandez-Flores, MD, PhD, S. Patología Celular, Clinica Ponferrada, Avenida Galicia 1, 24400 Ponferrada, Spain; Phone (00 34) 987 42 37 32, Fax (00 34) 987 42 91 02, e-mail: gpyauflowerlion@terra.es

Received: September 5th, 2009

Accepted: January 10th, 2010