Rhinopharyngeal necrotizing granuloma: the beginning of Wegener's granulomatosis

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SUMMARY

The clinical onset of rhinogenal Wegener's Granulomatosis is a necrotizing inflammation of the rhinopharinx with haemorragic tendency, referred to as "Rhinophayngeal Necrotizing Granuloma" (RNG). It has a subdolous evolution and it generally manifests itself through indirect signs involving the posterior nasal-paranasal region and/or the middle ear.

It is probably due to drug hypersensitivity or to immune complexes and this, together with the different anatomo-clinical picture, distinguishes it from the more frequent idiopathic Granuloma gangraenescens. The diagnosis of RNG is fundamental in trying to stop the dramatic evolution of the disease to vasculitis and diffuse granulomatosis, but this may be very difficult if one doesn't bear in mind this process in his clinical practice.

Two personal observations are briefly reported together with their ultrastructural study which proved to be useful for a more rapid exclusion of other possible granulomata. The corticosteroid therapy has, in the first case at least, succeeded in blocking the course of the disease.

IN 1939 the German pathologist F. Wegener described a disease, today considered to belong to the polymorphic group of panarteritis nodosa (Godman and Churg, 1954), which is characterized in its complete or rhinogenal form by 1) an initial nasal feverishness which leads towards a progressive involvement of the respiratory tract; 2) scattered necrotizing vasculites and 3) scattered granulomata with nephritis responsible for exitus (Wegener, 1939, 1970).

In 1957, with G. Ferreri, we presented the first case of this disease to be diagnosed in the Italian ORL field. It could be due to hypersensitivity to phenylbutazone, that is to an immunological mechanism of Coombs and Gell's 2nd type (1964) according to the pathogenetic interpretation of some of the thirty-two cases reported hitherto in the literature. In that occasion we thought it convenient to emphasize that the identification of the initial nasal lesion was exclusively up to the rhinologist. Furthermore, we stated that, in order to adopt a therapy capable of blocking the dramatic evolution of Wegener's disease, this process must be considered in differential naso-pharyngeal diagnostics.

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The initial nasal process involves the rhino-pharynx and it easily spreads towards the posterior portion of the rhino-sinusal complex, manifesting therefore itself with indirect signs, sometimes also with middle otitis. It was denominated by us Rhinopharyngeal Necrotizing Granuloma (RNG) and it appears as a necrotizing inflammation with a tendency to haemorrage and spread, during the course of feverish attacks, progressively downwards along the respiratory tree. This clinical characteristic, together with the histopathological picture in which were observed scattered giant cells, diffuse necrotizing vasculitis and eosinophils, suggested, more lately (Ferreri and Crifo', 1960), a formal distinction between RNG and idiopathic Granuloma gangraenescens, which was submitted again to the attention of rhinologists by the important studies of I. Friedmann (1955) and M. Arslan (1958). This distinction, initially intended to avoid a diagnostic confusion and, according to Wegener himself (1939), to "facilitate future aetiological researches", seems today confirmed by new various acquisitions. In fact, idiopathic Granuloma gangraenescens must be considered as an essentially localized process with possible focal potentiality (Crifo', 1964). It occurs in middle aged persons of both sexes and it likely has at its basis an immune mechanism of Coombs and Gell's 4th type, in other words associated to delayed hypersensitivity (Crifo', 1958; Friedmann, 1964; Manara and Procerutti, 1968). From a clinical point of view idiopathic Granuloma gangraenescens possesses a marked tendency to evolve towards the exterior, ulcerating the midline of the face *(middline form)* or the palate *(palatine form)* or, more rarely, the internal corner of the orbita *(pseudotumor orbitae)*, as we have had the opportunity to observe personally (Crifo', 1957; Ferreri and alii., 1959; Crifo' and alii., 1971). Morphologically, this process is backed up by a granulation tissue apparently devoid of specific marks (Friedmann, 1955), the ultrastructural details of which we have recently analyzed (Crifo' and alii., 1971). Furthermore, while the rare autopsies made on these patients, at least those we directly know, have never showed visceral lesions (Cherubino, 1959; Crifo', unpublished obs.); only in some cases microscopic angitis and kidney lesions were demonstrated. In our opinion, these atypical cases could be explained with a metafocal mechanism.

The above observations suggest a distinction between RNG, which is the first expression of a systemic disease, and idiopathic Granuloma gangraenescens, an essentially localized lesion.

As already reported, the main problem with rhinogenal Wegener's Granulomatosis is to achieve an early diagnosis through the identification of RNG which represents its first clinical manifestation. But as the former is a very rare disease and the latter has very alarm simptoms, such an early diagnosis may be very difficult. In the last few years we have had the opportunity to study several patients, directed to us by Colleagues or Practitioners, for suspected Granuloma gangraenescens or Wegener's granulomatosis. In two cases we diagnosed RNG.

Our first observation dates back to the end of the year 1967 and was communicated at the 67th Congress of the French Society of Otorhinolaryngology (Crifo', 1970). Our second case dates back to the end of the year 1970 and is still under control, internistical as well. These two observations, that we shall outline further on,

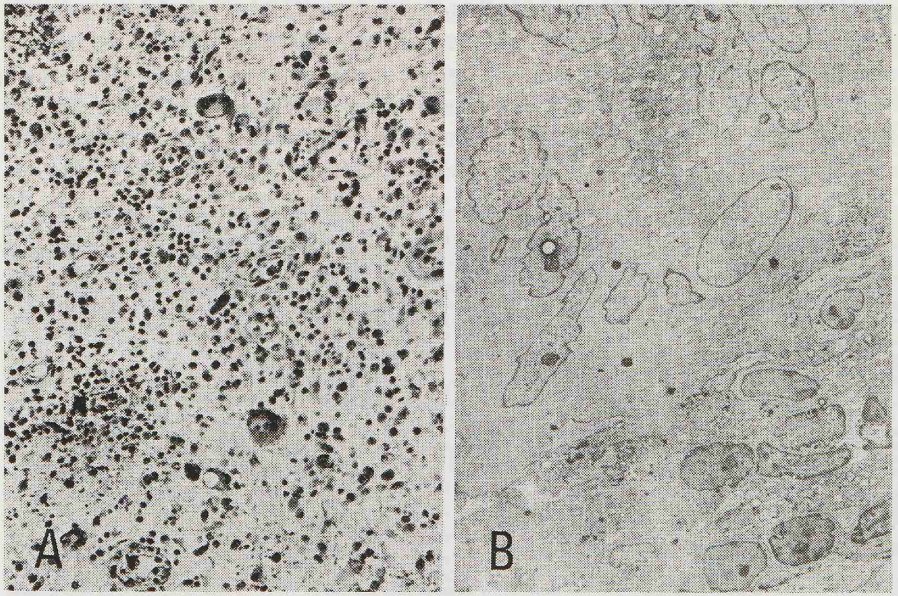

Figure 1. Rhinopharyngeal Necrotizing Granuloma. Obs. I.
A: Evidence of scattered giant cells and angitis (100 x).
B: Ultrastructural detail of portion of a gaint cell (1600 x).

show that an early diagnosis of RNG is possible and that thanks to it, Wegener's disease can be effectively blocked in its dramatic evolution.

CLINICAL OBSERVATIONS

The first case concerns a young man of 20 who on admittance to this Department already had a complex clinical history. The apparent onset was a relapsing feverish angina refractory to the common antibiotics. An otitis media manifested itself later on and, finally, during the course of the last recurrence, papulo-nodular elements appeared in the limbs. A previous admittance to another hospital had brought, on the basis of a biopsy, to a diagnosis of tubercolosis of the pharynx, without radiologically ascertained pulmonary lesions. The specific therapy carried on for several months, didn't improve his conditions; on the contrary, the recurrences had become comparatively more frequent with costantly concurrent papulo-nodular eruptions in the limbs and, finally, also by a fairly haemorragic nephritis, which apparently recovered with simtomatic therapy.

On admittance to this Department, the involvement of the rhinopharynx seemed important and the necrotizing character of the lesion, with a tendency to haemorrage at the touch, drew our attention. All the researches were therefore oriented to demonstrate that it might have been a RNG. A tubercular aetiology, as other possible specific causes, was excluded after appropriate and repeated laboratory examinations; the conclusive results for the diagnosis of RNG were, however, reached thanks to the histopathological study of the rhinopharyngeal lesion and the results of the intense corticosteroid therapy. The former was carried out down

at the ultrastructural level, combining also some immunofluorescence techniques: it demonstrated that the lesion was characterized by giant cells, even young, scattered in the inflammatory tissue (Figure 1a, b) and by a damage of the small vessels of any kind (Figure 2) with the presence of eosinophils, particularly at their periphery. On the other hand, immuno-fluorescence showed numerous IgG cells and less IgA-positive elements, and the presence of complement beta-1-C fraction and fibrin at the level of the walls of many inflammatory vessels. In

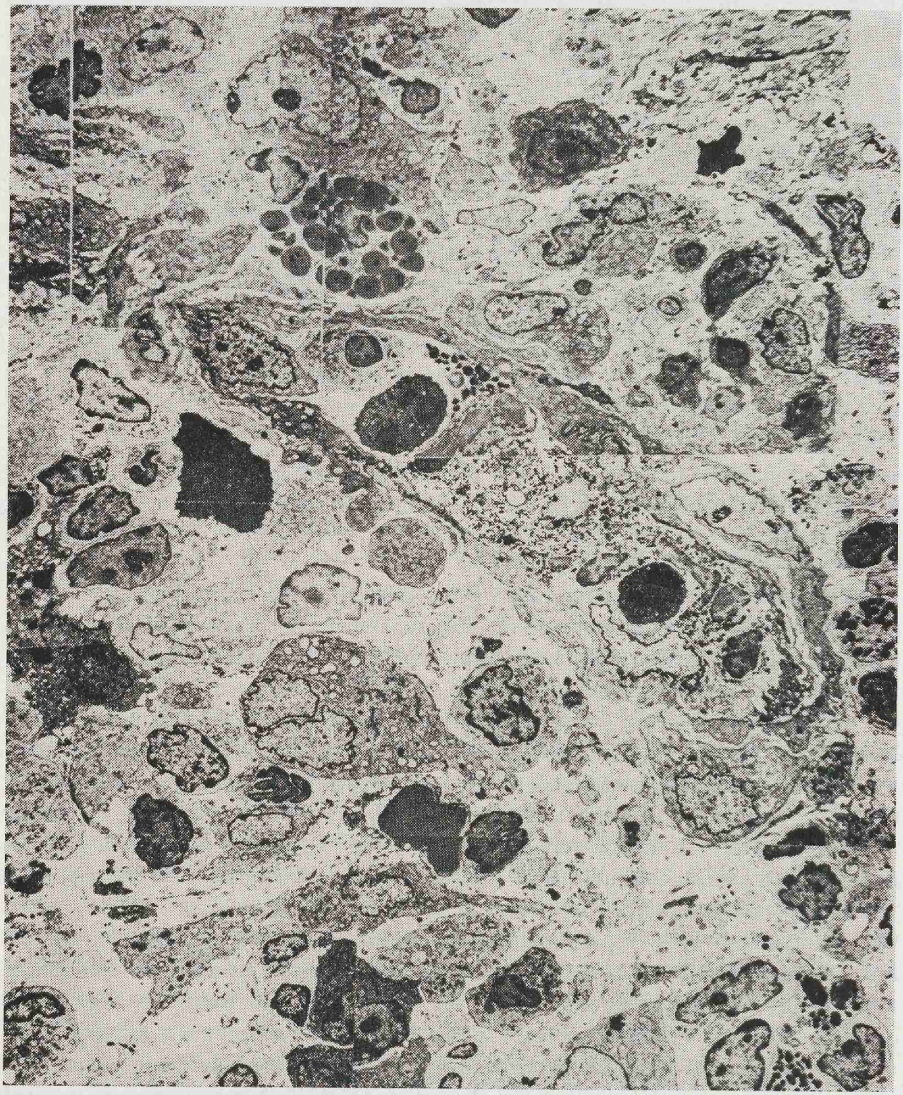

Figure 2. Rhinopharyngeal Necrotizing Granuloma. Obs. I.
Ultrastructural picture showing the necrotizing inflammation of a small vessel with marked pleomorphism of the exudating cells (2000 x).

other words, the immuno-histo-chemical picture showed several characteristics suggesting an immune-complexes mechanism. The response to therapy was exciting: after a few days since the administration of high doses of corticosteroids was started, the pain had gone, the pharynx was deterged and the skin lesions had regressed, and after about two weeks the pharyngeal lesion already appeared completely healed.

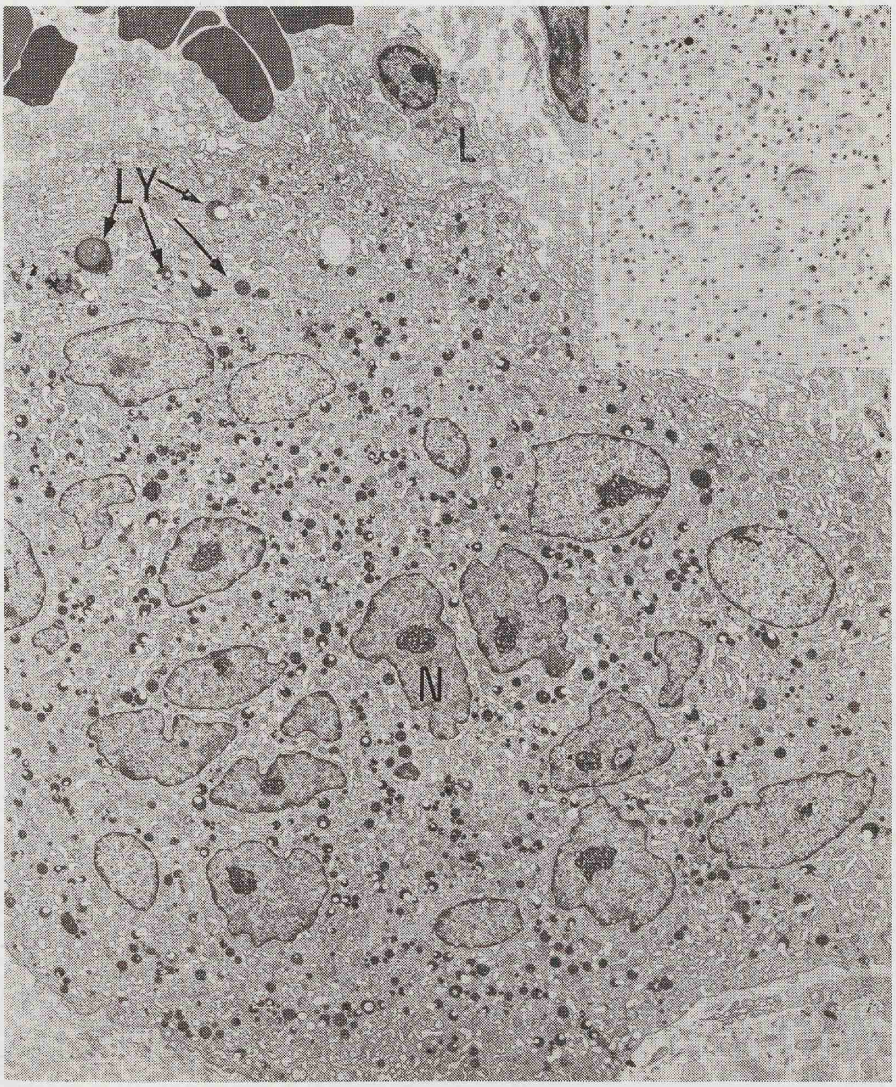

Figure 3. Rhinopharyngeal Necrotizing Granuloma. Obs. II.
The insert shows the inflammatory tissue with several giant cells (100 x). The ultrastructural detail shows a portion of one of these cells with nuclei even centrally located (N), and numerous lysosomes (LY). L: lymphocyte (2800 x).

The patient was dismissed after a few weeks, and since then he has been monthly checked from a clinical and radiological viewpoint with blood tests, as he is still maintained under corticosteroid therapy. During this prolonged period of control he presented at least four localized recurrences, always with the common necrotic-haemorragic characters, which were each time overcome by intensifying the anti-reactional therapy. During the periods of apparent well-being, the while during

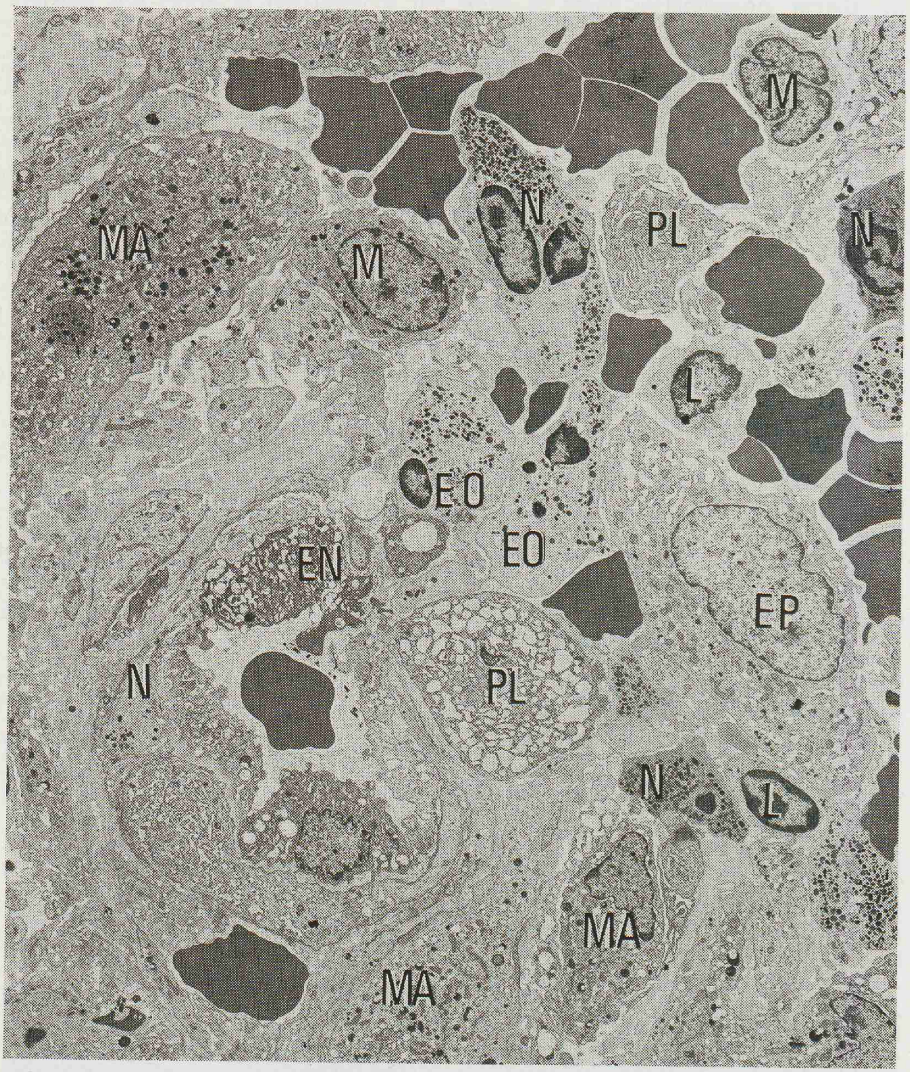

Figure 4. Rhinopharyngeal Necrotizing Granuloma. Obs. II.
Exudative-necrotizing vasculitis. The endothelium (EN) is swollen and partly damaged. Around the vessel neutrophils (N), monocytes (M), macrophages (MA), lymphoid elements (L), plasma cells (PL), epithelioid cells (EP), and eosinophils (EO) can be seen (3200 x).

the crises the aspecific signs of immune reactivation were always found, that is hyperleucocytosis with relative neutrophilia, increased Katz's index, hypergammaglobulinemia with high degree of aspecific IgE, and marked positivity of the test for reactive protein C. The patient has left our city eight months ago for work reasons and is now medically assisted in his new place of residence. According to the information we had about three months ago, he is in satisfactory conditions. The second case concerns a 27 years old woman, who presented, about three months after her second physiological pregnancy, episodes of feverish rhinosinusitis which brought her to hospital several times for bilateral Caldwell-Luc operation and for an unexplainable postoperatory unsatisfactoriness. The appearance of sudden dyspnea with disphonia required an urgent recovery to this Department for tracheostomy. The clinical examination demonstrated hypoglottic stenosis and irregular healings of the anterior portion of the nasal fossae. These masked a necrotizing haemorragic process of the posterior portion and of the rhinopharynx. In this case, though conclusive anamnestic elements were lacking, we even thought about a rhinoscleroma; but this aetiology was excluded by the researches, and RNG was diagnosed primarily on the basis of the microscopic features of the rhinopharingeal lesion. Figure 3 shows in the insert the typical picture of RNG: evenly distributed giant cells outstand among other inflammatory elements infiltrating the chorion of the mucosa. The ultrastructural detail shows the fine morphology of a giant cell, with several nuclei even centrally located and many lysosomes as Friedmann already observed (1964). The second characterizing element is the necrotico-haemorragic angitis (Figure 4). We can see endothelial lesion and infiltration of the wall by pleomorphic cells, i.e. neutrophils, limphomonocytes and eosinophils. Furthermore, at the periphery of the vessels, red cells, plasma cells, some eosinophils, several monocytes and macrophages and few epitelioid cells can be observed.

A strong antireactional and antibiotical therapy was immediately effected but, after an initial satisfactory response, a new feverish attack, arisen after two months with the usual signs of hyperleucocytosis with neutrophilia, hypergammaglobulinemia with high IgE rate, increased Katz's index and high positivity of the test for reactive protein C, wasn't opposed by high dosages of corticosteroids. The patient was therefore directed to the Department of General Medicine for an immune-depressive therapy. According to what we have learnt, this treatment has had limited results and, at present, the patient's conditions are not very satisfactory.

CONCLUSIONS

As demonstrated by the two observations we have reported, an early diagnosis of Wegener's rhinogenal Granulomatosis through the identification of its initial process or RNG, though extremely complicated for the rarity and rapid evolution of the disease itself, is possible. It is based on the finding of a necrotizing inflammation of the rinopharynx, tendencially haemorragic: it usually spreads towards the posterior nasal-paranasal region and is at times associated to auricolar symptoms. The anamnestic data, the clinical examination and particularly the histological observation of

giant cells, necrotizing vasculitis and eosinophils can draw to a diagnosis of RNG. The differential diagnosis should particularly be made with idiopathic Granuloma gangraenescens and with other Granulomata: i.e. in the two reported cases, with tuberculosis and rhinoscleroma. A rapid differentiation can be gained with electron microscopic study which can show the absence of specific agents confirming the typical RNG's picture. Furthermore, for diagnostic purpose the results of the corticosteroid and/or immune-depressive therapy can be very important, as in our first patient.

The diagnosis of RNG is up to the Rhinologist and is the only way in trying to stop the evolution of a disease that until a few years ago was rapidly fatal. But it may come possible only taking always into consideration the rare RNG in differential diagnostics.

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