# Wegener's Granulomatosis

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Recently, there is an increasing number of literatures[1-10] concerning Wegener's granulomatosis, but yet the exact cause remains obscure and successful treatment doubtful.

This condition clinically shows three phases as follows:

1. A prodromal period with signs of rhinitis and ulceration of the upper respiratory tract.
2. A second stage of acute dissemination with development of pulmonary disease as part of a diffuse vasculitis also affection spleen, liver, nervous system, and other organs.
3. Final stage of glomerulonephritis with terminal uremia.

One case is reported in which authors have made a probable diagnosis of Wegener's granulomatosis in the prodromal period, and later confirmed.

## REPORT OF A CASE

The patient, a 21 year-old female, was referred to our Department by an otolaryngologist on March 8, 1968, with a history of a nasal stuffiness on the left side for two months or more, and directly admitted to the Hospital. She first noticed the unilateral nasal obstruction in the mid Dec. 1967, later associating a slight nasal hemorrhage on the same side which dominantly occured in morning. In the beginning of Feb. 1968, she suffered from common cold which subsided within one week, and since that time the nasal obstruction became intensified, but there were no troubles of nasal and postnasal discharges and headache. On Feb. 26, 1968, she was examined by the otolaryngologist Who, in answer to our inquiry, reported that when first examined her the mucosa of the nasal cavities was markedly hyperaemic and an ulcer was seen on the anterior tip of the left inferior turbinate. He also explained that each middle turbinate, at that time, was not necrotic but hyperaemic, even though it became necrotic being covered with fur and crust since March, 5. Following day first examined her, he performed a biopsy on the ulcer. The histological record was

an inflammatory granuloma without any neoplams.
Prior to the onset of the present evidence, she always enjoyed good health and there was no history of any allergic disorders.

Physical examination revealed a young woman who was not febrile and did not appear acutely ill. On auscultation, no rales was there on the chest. Neither liver nor spleen was palpable.

Local examination disclosed a severe hyperaemia of the mucosa of the nostrils, particulary inferior turbinates and septum, an ulcer on the tip of the left inferior turbinate as shown by Fig. 1, and necrotic change of middle turbinates which were demonstrated by both anterior and posterior rhinoscopies. In the oral cavity, pharynx, and larynx no pathologic changes were observed. No adenopathy was detected on the neck.

A x-ray examination of the chest done on March 9, showed an almostly normal appearance. X-ray of the nose and paranasel sinuses, including tomographs, revealed a diffusely moderate cloudiness on both maxillary sinus, but did not revealed any destruction of the bone (Fig. 2).

Biopsies were done on the ulcer lesion of the left inferior turbinate and both necrotized middle turbinates, revealed a distinct necrotizing and granulomatous inflammation with necrotizing vasculitis and infiltrations of plasma cells, eosinophils, giant cells, and other inflammatory cells (Fig. 3, 4).

Urinalysis done on March 11, revealed neither albumiuria nor hematuria. The erythrocytic sedimentation rates were 47 mm/1 hour and 75 mm/2 hours. The hematocrit was 40 per cent; red cell count $435 \times 10^4$, white cell count 9500, with 83.0 per cent segmented neutrophiles, 17.0 per cent lymphocytes, 1.0 per cent monocytes, and 0.5 per cent basophiles. Systematic blood chemistry tested on March 11, showed a normal pattern. The serum protein paper electrophoresis performed on March 11, showed a slight increases of $\alpha_2$ and $\beta$ fractions and a broad type's gamma globulin fraction. The immunoelectrophoretic pattern of the same serum indicated more distinct precipitation lines of transferrin and immuno-globulin-G (IgG) than those of normal serum. Fluid examination for electrolytes was in normal. CRP and RA tests revealed 1 grade positive, ASLO test 50 units and LE test negative. Serologic test for syphilis was negative.

Laboratory data of these tests done during her hospital course were illustrated by Tables 1, 2, 3 and 4.

Table 1. Urinalysis

| | protein | urobilinogen | sugar | red blood cell/field | white blood cell/field | epitherial cell/field |
|---|---|---|---|---|---|---|
| March 11 | − | + | − | − | − | − |
| March 12 | − | − | − | 2−3 | 7−8 | 3−4 |
| March 18 | − | ± | − | − | − | − |
| March 27 | ± | ++ | − | 2 | 5 | 5−6 |
| April 1 | − | + | − | − | 3−4 | 4−5 |
| April 4 | − | ++ | − | 1 | 4−5 | 4−5 |
| April 8 | +(30mg/dl) | + | − | 2 | 5 | − |
| April 11 | +(30mg/dl) | ++ | − | 5−6 | 15 | 8 |
| April 12 | − | ++ | − | 3 | 5 | 4 |
| April 15 | − | + | − | − | 2 | 3 |
| April 17 | − | + | − | 1 | 2 | 1 |
| April 23 | − | + | − | 1 | 1 | − |
| April 25 | − | + | − | 1 | 5−6 | − |
| April 30 | +(30mg/dl) | ++ | − | − | − | − |
| May 7 | − | − | − | − | − | − |
| May 8 | − | + | − | 2−3 | 5−10 | 1 |
| May 13 | − | ++ | − | − | 3−5 | 1−2 |
| May 17 | +(20mg/dl) | ++ | − | − | 10〉 | 1 |
| May 21 | − | − | − | − | − | − |
| May 23 | − | − | − | 1 | 6−7 | 2−3 |

Table 2. Examination of the Peripheral Blood

| | Hematocrit (%) | RBC | WBC | N. Myel. (%) | W. Metamyel. (%) | N. Band (%) | N.Seg. (%) | Eosioph. (%) | Basoph. (%) | Lymph. (%) | Monocyet (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| March 11 | 40 | $435\times10^4$ | 9,500 | 0 | 0 | 0 | 83.0 | 0 | 0.5 | 17.0 | 1.0 |
| March 25 | 39 | $429\times10^4$ | 18,500 | 0 | 0 | 0 | 83.5 | 3.5 | 0.5 | 9.0 | 3.5 |
| April 8 | 34.5 | $379\times10^4$ | 25,300 | 2.0 | 1.0 | 10.5 | 70.0 | 10.0 | 0 | 3.0 | 3.5 |
| April 15 | 25.8 | $294\times10^4$ | 19,600 | 1.0 | 0.5 | 7.5 | 73.5 | 9.0 | 0 | 8.5 | 0 |
| April 24 | 21.8 | $254\times10^4$ | 16,300 | 3.0 | 1.0 | 2.0 | 82.5 | 4.0 | 0 | 6.5 | 1.0 |
| May 1 | 27.5 | $334\times10^4$ | 18,900 | 1.0 | 1.5 | 9.0 | 77.0 | 2.5 | 0 | 7.5 | 1.5 |
| May 13 | 29.0 | $336\times10^4$ | 12,300 | 0.5 | 0 | 14.0 | 77.5 | 2.5 | 0 | 3.0 | 2.5 |

Table 3. Blood Chemical Tests

| | hemoglobin (g/dl) | serum protein (g/dl) | blood sugar (mg/dl) | A/G ratio | icteric index | C.C.F.T. | cholineste-rase(△pH) | alk. phosph. (u) | cholesterol (mg/dl) | G.P.T. | N.P.N. (mg/dl) | urea N (mg/dl) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| March 11 | 13.0 | 7.9 | 90 | 0.98 | 7 | 0 | 0.76 | 3.1 | 146 | 2 | 24 | 9 |
| March 25 | 12.7 | 7.5 | 80 | 0.67 | 9 | 0 | 0.66 | 2.4 | 180 | 3 | 26 | 12 |
| April 1 | 12.5 | 7.3 | 122 | 0.49 | 10 | 1 | 0.50 | 3.8 | 154 | 13 | 34 | 18 |
| April 15 | 7.4 | 5.0 | 126 | 0.39 | 4 | 2 | 0.23 | 4.2 | 110 | 8 | 15 | 7 |
| April 30 | 7.4 | 5.8 | 88 | 0.45 | 4 | 1 | 0.24 | 4.4 | 111 | 3 | 21 | 9 |
| May 13 | 8.6 | 5.3 | 88 | 0.43 | 4 | 1 | 0.20 | 4.7 | 126 | 5 | 20 | 8 |

Table 4. Serologic and Serum Chemical Tests

| | erythrocytic sedimentation rate: | |
|---|---|---|
| March 9 | 47 mm/1 hour | 75 mm/2 hours |
| March 25 | 88 mm/1 hour | 113 mm/2 hours |
| April 8 | 48 mm/1 hour | 44 mm/2 hours |

| | CRP | RA | ASLO | LE tests |
|---|---|---|---|---|
| March 12 | 1 + | + | 50 u. | − |
| April 11 | 6 + | ++ | 12 u. | − |
| May 14 | 6 + | ++ | 333 u. | − |

paper electrophoresis of serum protein

| | alb. | $\alpha_1$ | $\alpha_2$ | $\beta$ | $\gamma$ |
|---|---|---|---|---|---|
| March 13 | 49.4 | 5.5 | 10.6 | 12.8 | 21.7 |
| April 12 | 29.4 | 12.5 | 19.4 | 15.7 | 23.0 |

We tentatively made the diagnosis of Wegener's granulomatosis on the ground of the acute rhinitic manifestation with an ulcer lesion which showed a necrotizing granulomatous inflammation with angitis in microscopic examination and abnormal rates of the erythrocytic sedimentation.

Steroid therapy in the form of 20 mg of prednisone daily was begun from March 11, together administration of Ilotycin 1.0 g. daily and radium irradiation on both middle meatuses, latter totally 650 $\gamma$. During the first two weeks she was comfortable afebrile and apparently in normal health, and improved with less nasal obstruction and bleeding. Objectively, both nostrils were well meatuses and the hyperaemia of the nasal mucosa reduced, however the ulcer lesion of the left inferior turbinate and necrotic change of middle turbinates were not repaired. Since March 23, the nasal obstruction again increased associating with serous nasal discharge later changed to purulent. Nasal mucosa was markedly

so swollen that the nostrils were complete obstructed. At that time she complained of a cough, so the chest was examined by x-ray films whichdisclosed a round shadow on the middle portion of the right lung as shown by Fig. 5.

A few days later she became to be febrile with predominant cough, itches on the hands, and a severe earache on the left side (otoscopically detected an acute middle ear infection). On March 28, the cough increased associating with dyspnea and intensifying sore throat. Many papules, like erythema exsudativum multiforme, appeared on the lower extremities with itch and pain (Fig. 6). A biopsy specimen taken from one of these papules showed a picture of subacute dermatitis characterized by round cell infiltration (Fig. 7). She had a painful swelling around the joints of extremities. At that time distinct rales were easily demonstrated on the right sided lung. In the oral cavity, there were several ulcers coated with yellow fur on the midline portion of the soft palate near the uvula mainly and around the anterior pillar of the tonsils on both sides.

We considered these symptoms due to acute dissemination of the disease, therefore decadron was given daily 8 mg intramusculary during following three days. On April lst, 2nd, and 3rd, the fever abated, however she was repeatedly attacked by severe abdominal pains with diarrhaes which were controled only by narcotics. At that time stool guaiac was positive in high grade for four days. These abdominal pains might be caused by intestinal hemorrhages, although it was obscure whether the hemorrhages were due to steroid drugs or acute dissemination of the disease. The daily doses of prednisone and decadron were reduced gradually to 10 mg and 2 mg.

The pains began to cease since April 5, but the sore throat and pain of the extremities's joints remained. Soon later hoarseness appeared and advanced to complicate dysphonis. A mirror examination detected a small ulcer on the mid portion of the left true cord. Both hoarseness and dysphonia continued through her all hospital course.

Renal biopsy was considered but not forgone because albumiuria and hematuria were not presented or very few, and urea N and N.P.N. in serium not increased. The daily dose of decadron and prednisone was reduced gradually to 2 mg and 10mg.

X-ray examination of the chest on April 10, showed a large tumor like shadow which occupied the middle portion of the right lung (Fig. 8).

The paper electrophoresis performed on April 12, demonstrated that the relative concentration of $\alpha_2$ fraction in serum was markedly increased. This increase mainly depended on an increase of haptoglobin as shown by a further examination of disc electrophoresis (Fig. 9).

Many papules almostly disappeared until April 15, and she was free from the discomport of severe abdominal pain, cough, and complete nasal brockage, but

gradually was getting worse and emaciated. Her appetite also decreased. Examinations of the peripheral blood done after April 15, constantly revealed a moderate anemia, so blood transfusion of 200ml. was performed twice on May 7 and 10 without improving her general condition. Since May 15, the cough reappeared with chest pains. Ulcer lesion of the soft palate progressed and destroyed the uvula entirely.

On May 28, she was discharged from the Hospital as being not improved in accordance with her family's wish.

## COMMENT

It is well known that Wegener's granulomatosis is an extreme malignant disease with death on average in a period of four to six months.[2)7)17)]

In many cases, especially in earlier reports, the diagnosis has been established most frequently by postmortan observations or late in the period of final stage, because this condition has a rapid course and shows diversely clinical features. The case reported here was recognized at its early stage. This is rare.

The etiology of this disease is not known. However, many authors, as well as Wegener[11)] who is one of the first reporters of this disease, are of opinion that this lesion is a disease of hypersensitivity (which is a common disturbance in immunity) for reason of that the triad finding of Wegener's granulomatosis as granulomas, necrotizing arteritis, and glomerulitis may be found in hypersensitive states as defined by Rich, according to DeOreo[9)]. Kenney et al[8)] mentioned that the dramatic response to steroids lends support to the role of hypersensitivity in this disease.

Budzilovich et al[10)] and Godman et at[12)] suggested an infectious etiology, and later Sharnoff et al[7)] reported one case which is suggestive to support this theory. Godman et al[12)] considered that the respiratory tract may represent "the primary locus of attack of a noxious agent, probably microbial, "which incites the granulomatous inflammation locally, and then the continuous association of the host's tissue in the sites of the initial involvment with the agent leads to a high degree of local tissue hypersensitivity. Advent of generalized hypersensitivity to the offending agent results in dissemination of the lesions. However, Kinney et al[8)] stated that neither in the cases reported in the literature nor in the bacteriologic studies of tissue from their 2 patients were microorganisms found that were considered etiologically significant. Blatt et al[13)] suggested that the intial disease in the respiratory tract may be caused by any of a variety of noxious agents, as chemical irritant, physical agent, or infectious organism, and that the disseminated lesions which follow may be produced by a tissue autoantigen-antibody mechanism. A similiar consideration was made

by DeOreo[9] who suggests that initial ulcer of the respiratory tract acts as a preparatory or sensitizing dose, and the hematogenous dissemination of toxins and/or breakdown products of the host's altered tissue proteins provides the shocking or challenging dose which results in wide-spread tissue reaction in the vascular structure of the lungs, kidenys, spleen, and other organs. This may be a clinical counterpart of the experimentally produced reaction known as the Sanarelli-Shwarzman phenomen.[14][15] Parker[6] mentioned that physicians have tried to elicit a history of drug allergy to explained the etiology of Wegener's granulomatosis and periarteritis nodosa, because patients with the former condition, in particular, have frequently received antibiotics or sulfonamides early in the course of their disease. He also said that the problem is in deciding involvment were actually due to Wegener's granulomatosis, and the antibiotic or sulfonamide therapy incidental, or whether there was a bacterial or viral infection of the upper respratory tract for which these drugs were given, following which Wegener's granulomatosis developed as manifestation of drug allergy. One of two cases reported by Kinney et al[8] showed a severe urticartial reaction to penicillin occured early in the course of the acute and terminal phase of his disease. They, but explained of that the relationship existed between the use of penicillin and the disease process is speculative.

Most similar diseases to Wegener's granulomatosis are periarteritis (poriarteritis) nodosa and lethal midline granuloma. Opinions differ on entities of these disease and Wegener's granulomatosis. Blatt et al[13] suggested that 2 entities of Wegener's granulomatosis and lethal midline granuloma, which they term "generalized rhinopharyngological systemic syndrome"(Wegener's granulomatosis) and "localized rhinopharyngological syndrome" (lethal midline granuloma), are the same disease process. Fienberg[16] proposed that Wegener's granulomatosis and other related conditions are manifestations of disseminated or focal pathergic granulomatosis, implying the total effects induced by altered reactivity. However, Yarington et al[2], Kinney et al[8] and Walton[17] considered Wegener's granulomatosis to be separable from lethal midline granuloma because of lacking of distinctive granulomatous and vascular lesions and of their dissemination in the latter condition. Walton[17] and Burton[18] noted that many reported cases at first considered to be examples of lethal midline granuloma were found subsequently to be associated with an underlying malignant process, particularly reticulum-cell sarcoma, which always must be considered in patients with necrotinzing nasopharyngeal lesions.

Most distinct differences between Wegener's granulomatosis and periarteritis nodosa are the presence of hypertension and the less involvement of the lungs and spleen in the latter condition. Wegener[11] first thought of this condition to be a variant of periarteritis nodosa, and many authors agreed with Wegener, whereas Yarington et al[2] and Walton[19] stated that the entity of this disease

is distinct and differs from periarteritis nodosa.

Although the true cause of Wegener's granulomatosis is not clear as mentioned above, authors consider that it may occur in patient who has a disposition exhibiting hypersensitivity and is attacked by noxious agents, yet unknown, resulting injuried the upper respiratory tract, which may seem to be a trigger to following disseminated manifestations.

Authors think, as do Kinney et al[8], that earlier diagnosis will be gained only by clinical awareness of this disease and adequate biopsy of respiratory lesion in suspected cases.

Test of the erythrocytic sedimentation rate is very useful as a screening test.

Authors regard that the scantiness of the renal symptoms in our case is due to the steroids therapy begun from the early stage.

## SUMMARY

A case of Wegener's Granulomatosis was added, which was diagnosed in the prodromal stage. Though steroid therapy, antibiotics and radium irradiation were begun from the early stage, manifestations of acute dissemmation appeared and she gradually getting worse. Etiology of this condition was discussed.

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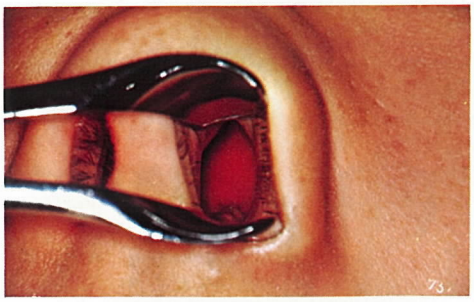

Fig. 1. Photograph of the left nostril, showing a ulcer lesion of the inferior turbinate and a severe hyperaemia of the mucosa.

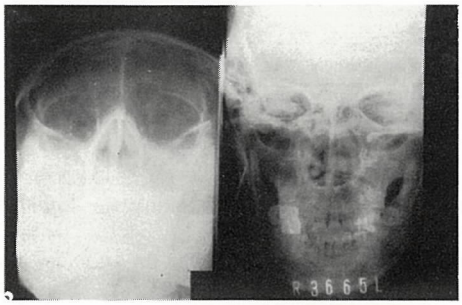

Fig. 2. X-Ray examination of the nose, showing a diffusely moderate cloudiness on both maxillary sinus and no bony destruction.

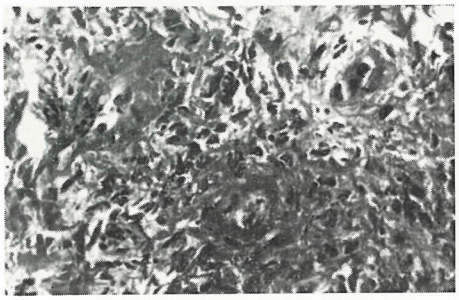

Fig. 3. Histologic picture of the specimen taken from the ulcer of the left inferior turbinate, showing notable vasculitis. (H.E. ×400)

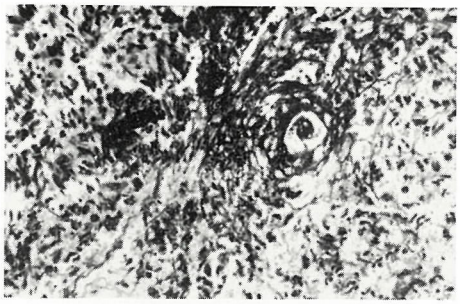

Fig. 4. Histologic picture of the same specimen to the Fig. 3, stained with PTAH (×400)

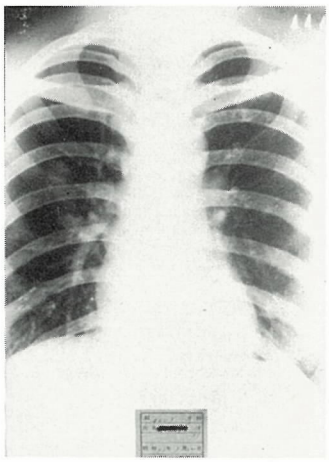

Fig. 5. X-Ray examinatino of the chest done on May 22, showing a round shadow on the middle portion of the right lung.

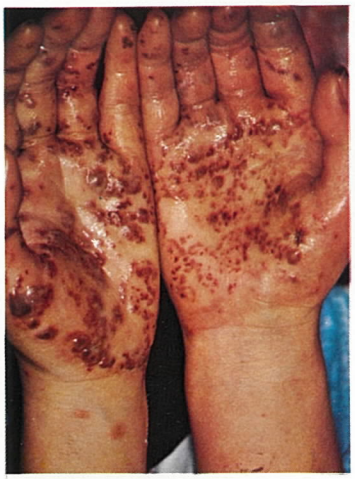

Fig. 6. Photograph of papules like to erythema exsudativum multiforme.

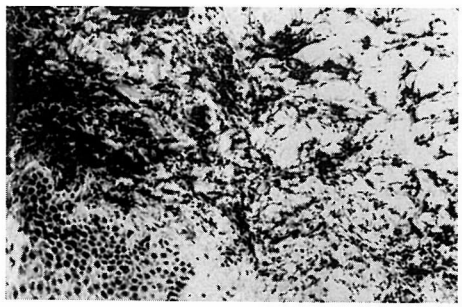

Fig. 7. Histologic picture of the specimen taken from one of the papules, showing the findings of subacute dermatitis characterized by round cell infiltration.

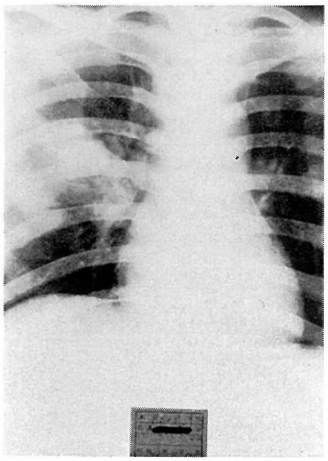

Fig. 8. X-Ray examination of the chest done on April 10, showing large tumor like shadows on the middle portion of the right lung.

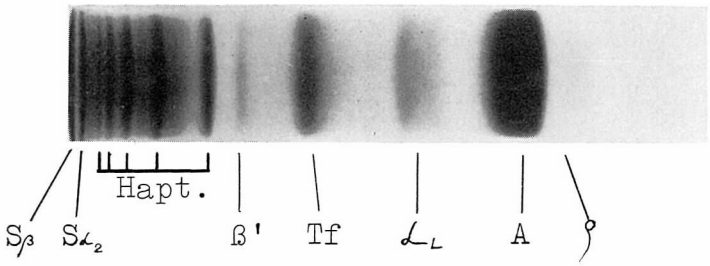


Fig. 9. Disc Electrophoregram of the serum, showing distinct haptglobin fractions.