Loeffler’s Syndrome (Transient Pulmonary Infiltrations with Eosinophilia) **

Report of a Case and a Review of the Available Literature

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HISTORICAL

In 1932, William Loeffler, 1 Professor of Medicine at the University of Zurich, described the syndrome that bears his name. Briefly described, the syndrome is characterized by a mild group of symptoms, a scarcity of physical signs, a blood eosinophilia varying from less than 10 per cent to more than 60 per cent, a benign course and spontaneous healing usually within a period of two to three weeks.

Since his description, there have been relatively frequent reports of cases almost all of which have shown so striking a similarity in symptomatology, physical, x-ray and blood findings, that a definite entity has been recognized to which the name Loeffler’s Syndrome has been given. By 1936, Loeffler alone reported 51 cases, all from Switzerland. To date, case reports have appeared in the medical literature of the Scandinavian countries, France, Holland, Palestine, Canada, Spain, Germany, Italy, Britain, China, Japan, Hawaii, and from many of the South American countries. In this country, cases were reported by Soderling, 2 Smith and Alexander 3 in 1939, Stuart, 4 Freund and Samuelson 5 in 1940, Baer 6 in 1941, Hoff and Hicks 7 and Karan and Singer 8 in 1942, Smith 9 in 1943, Pirkle and Davin, 10 Slowey, 11 Peabody, 12 Ryan, 13 Jones and Sauders, 14 Hansen, Pruss and Goodman 28 in 1944, Miller, 29 and Hennel and Sussman 30 in 1945.

ETIOLOGY

An adequate explanation of the etiology is still lacking, probably because there is no uniform cause. Loeffler first thought that the condition might be a benign form of tuberculosis. However of the 37 cases tested with tuberculin, 13 were negative. He later considered the role played by parasites causing the condition and still later thought that the eosinophilia was an expression of an anaphylactic process.

A review of the literature to date leads one to the conclusion

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that tuberculosis can easily be dismissed as a causative factor.
The parasitic theory, however, must be considered in view of the numerous case reports, mainly in children, where a blood eosinophilia and transient pulmonary infiltrations were accompanied by intestinal parasites, such as amoebiasis,\textsuperscript{7} trichiniasis,\textsuperscript{11} and ascarides.\textsuperscript{13} Wild,\textsuperscript{14} who reported two cases of ascaris lumbricoides, thought that the larvae penetrated the intestinal wall and were carried by the portal vein or the thoracic duct to the right heart, thence to the right lung where they caused a local reaction with atelectasis and penetrated the alveoli and then were coughed or carried up and expectorated or swallowed. Case reports in the literature of Loeffler's syndrome associated with distomatose hepatic\textsuperscript{15} and necator americanis\textsuperscript{16} further strengthen the parasitic theory.

In addition to the parasitic theory, the allergic theory must, in the face of the accumulating evidence, receive serious consideration, since some of the cases of Loeffler's syndrome reported have been in individuals, often children, whose allergic symptoms such as vaso-motor rhinitis and especially asthma, led to the discovery of the condition.

Stefano\textsuperscript{17} reported a case of recurring asthmatic attacks in which transient areas of pulmonary infiltrations were demonstrated by x-ray and in which amoebae were found in the sputum but not in the stools. Both amoebae and asthma disappeared after treatment with emetine.

Engel\textsuperscript{18} of Shanghai should be credited with being the first to point out a definite allergic correlation. During the months of May and June, Engel noticed that for years a large proportion of the inhabitants of China were stricken by a peculiar bronchitis which in every day life is called "privet cough". Privet is the name of a species of ligustrum which flowers at the time mentioned. The complaint manifests itself in a cough of moderate intensity, with scanty yellow sputum having a metallic taste, and lasts only 2 days. Engel became interested in it because he suffered from it five years previous to his report. He therefore had x-rays made in the spring of two different years and on both occasions they revealed a massive pulmonary consolidation which completely cleared up after one day on one occasion and in 6 days on the second occasion. Blood showed eosinophilia from 20 to 25 per cent with an otherwise normal blood picture. At random, he chose one of his friends who complained of a similar cough and he showed the same things on x-ray, and cleared in 7 days. Engel reported two cases in 1935 and proposed the name of allergic pulmonary edema for the disease. On the basis of observations on more than 100 cases and reports in the literature, Maier\textsuperscript{19} is also convinced...
that temporary pulmonary infiltrations with blood eosinophilia are of an allergic nature.

Engel also was the first to point out, after studying Loeffler's cases, the very seasonal incidence. Most of the cases have been reported during the months of July and August. A smaller group of cases have been reported during the spring months. Almost two-thirds of the reported cases were in males, mostly adults. The condition has been reported in members of the same family.

The marked seasonal incidence and the epidemic form suggest an infectious agent as the cause of the condition and it is for this reason that one has to consider an atypical virus infection as the cause of the pulmonary infiltration which in re-absorbing would elicit eosinophilia since such a virus infection as dengue may cause rather marked eosinophilia.

Over-exposure to the sun has been mentioned in the literature as a cause of the condition by Gaines and Wieland.

Wieland suggested that climatic influences should be borne in mind; he stated that indiscreet and prolonged exposure to the sun may lead to transient congestive conditions in particular areas of the lung.

In summing up the conclusions in the more recent literature on the subject, one is led to the dominating view that allergic phenomena play a decisive role in the pathogenesis of Loeffler's disease.

**PATHOLOGY**

Since the clinical course in Loeffler's disease is mild, and since spontaneous healing takes place, autopsy material is rarely available. Obviously an accurate description of the pathologic process is not possible. While Smith and Alexander reported a case in a child seven years of age with autopsy findings, an analysis of the symptoms and physical findings leaves a doubt as to whether or not the child actually died from this disease.

According to Loeffler's early reports, the pathogenesis is similar to erythema nodosum, the lung reacting with an inflammatory exudate to a toxin.

Some authors regard the lung changes as due to lung emboli, infarcts, localized bronchial asthma or atelectasis.

Engel believes that a localizing allergic edema of the lungs is responsible for the entire picture.

Von Meyenburg maintains that the transient infiltrations represent an eosinophilic pneumonia. Based on four accidental deaths he found that the infiltrations were of pneumonic type with exudation into the alveoli and with eosinophilic infiltration of both the alveoli and the interstitial tissue. There was an inflammatory involvement of the pleura and of the interlobar fissures.
SYMPTOMS

Loeffler's syndrome in a typical case consists of a low grade fever, some cough with expectoration, some fatigue. Occasionally a metallic taste to the sputum exists; not infrequently the condition is accompanied by a mild pain in the chest. Not uncommonly asthmatic breathing is noted. On the whole, the course in a typical case is so benign that the condition is discovered in the course of a routine examination. Twenty-five per cent of all Loeffler's cases were discovered accidentally. It is the discrepancy between the benignity of the entire course and the striking objective findings in the blood and in the roentgenogram which is responsible for the mistakes in diagnosis. A form described by Lohr and Kindberg differs from Loeffler's type in that the acute symptoms are severe almost like those of a septic process and that the process is extremely protracted and persists for months. Kartagener describes a case which he regards as representative of a third type of eosinophilic infiltration. This form is characterized by chronicity and mildness of the symptoms. Whether the three types of eosinophilic infiltrations represent three varieties of the same disease or whether they are distinct entities is difficult to decide.

COMPLICATIONS

In one case mentioned by Karan and Singer, there was increased resistance in the pulmonary circulation resulting in right ventricular strain. With the absorption of the pulmonary exudate, the heart returned to normal size. A few cases have been reported with complicating pleural effusions. Asthma associated with or preceding the initial onset of Loeffler's syndrome has been reported. In the writer's case, asthma followed the initial attack of Loeffler's syndrome.

PHYSICAL SIGNS

The physical signs are few in number. Dullness on percussion and diminution of breath sounds over the involved area can be elicited. A few migratory rales have been noted. Generally speaking, there is a paucity of physical signs when compared with the extensiveness of the fluoroscopic and x-ray shadows.

LABORATORY FINDINGS

The outstanding laboratory finding is the blood eosinophilia which ranges from 10 to over 60 per cent. One case has been reported with an eosinophilia of 85 per cent. In some instances the eosinophilia reaches a peak when the pulmonary infiltrations had almost completely disappeared. Eosinophilia persisted in some of the cases for some time. There was no strict parallelism between
the extent of the eosinophilia and the pulmonary infiltrations. White cell counts varied from 8,000 to 15,000. Occasionally there was a leucocytosis up to 20,000. Sedimentation rate ranged from 8 to 15 mm. in one hour. In some a more rapid rate was observed. Sputum was negative for tuberculosis in all instances.

The shadows seen on x-ray have been variously described as follows:

1. Large, more or less irregularly outlined, densities which were unilateral or bilateral.
2. Small infraclavicular infiltrations of the type described by Assmann.
3. Multiple unilateral or bilateral circular densities.
4. Sharply defined densities situated in the right middle lobe.
5. Infiltrations indistinguishable from the adult type of pulmonary tuberculosis.
6. Homogenous or nodular densities.

The characteristic x-ray pictures described by Loeffler consists of consolidations which appear suddenly in various parts of the lung and disappear rapidly while others appear in another portion of the lung. The shadows are more frequently found in the lower lung fields near the diaphragm and vary in size. They disappear in approximately a week or two and usually leave only very fine fibrous star-shaped scars. In the writer's case (Figs. 1, 2, 4) the infiltrations seem peripherally placed on both sides.

**DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS**

The diagnosis of Loeffler's syndrome can only be made, first, by the blood eosinophilia; second, by the transient x-ray shadows and third, by the clinical course. An allergic history prior to onset of symptoms is an aid in diagnosis—positive stool findings, whether amoebae or other parasites, calls for blood studies and x-ray of chest. Frequently a definite diagnosis can only be made through the medium of serial x-ray films of the lungs and after the condition has subsided.

In the differential diagnosis the following conditions must be considered: pulmonary tuberculosis, pulmonary embolism with infarction, pneumonia, bronchial asthma with partial atelectasis, erythema nodosum and anything that causes fleeting pulmonary infiltrations, such as seen in virus respiratory infections.

**PROGNOSIS**

The prognosis is good. There is usually spontaneous disappearance of physical signs, x-ray shadows and blood eosinophilia in a period of a week to three weeks. A few cases have been reported where the condition lasted a longer period with delayed recovery.\textsuperscript{5,21,22}
TREATMENT

There is no specific treatment for the condition; it heals spontaneously. Emetine Hydrochloride—1 cc. intramuscularly for two days—where entamoeba was found was used by Hoff and Hicks. All symptoms disappeared after treatment with this drug, and stool was negative.

In December, 1937, Meyer reported eight cases, including one case which had sudden rhinitis, conjunctivitis and swelling of the face accompanied by eosinophilia and transitory lung infiltrations. He used calcium therapy and removal of contact from pollen to which patient gave a strong positive reaction, after which all symptoms and signs disappeared. Obviously in treating this condition successfully a search should be made for any allergen whether it be an intestinal parasite or pollen as a direct or indirect cause of the condition, and same removed with specific treatment for the parasites and removal from pollen. Bed-rest and symptomatic treatment will heal all other types of transient pulmonary infiltrations with eosinophilia. Weingarten in India, recently des-
cribed what he believes to be a new clinical entity manifested by severe paroxysmal bronchitis and a high eosinophilia in which arsenicals are a specific and quickly acting remedy.

CASE HISTORY

E. O. White, male, age 44, funeral director, reported for an examination on July 25, 1942, with the following complaints: fever varying from 99 to 101.5 in the afternoon; daily morning cough with expectoration of about a tablespoon of mucopurulent odorless sputum for the past month; weakness, loss of 15 pounds in the past 6 weeks, poor appetite.

Past History:

Patient stated that for the past 2 years he had a peculiar sensation in the chest, and for the past year he has been coughing. He stated that the cough left him for a few weeks after his nasal polyps were removed early in 1941. Three months after the first operation for nasal polyps a second operation was performed and more polyps were removed. Again the cough left him for a few weeks. Three weeks after the second operation he noticed difficulty in breathing. His physician informed him that he had bronchial disease. Throughout this time he had continued
treatments for the nasal condition. Early in January, 1942, he was operated on for a third time for recurrent polyps. He was again relieved of the cough for a short while. In May, 1942, a fourth operation was performed for polyps. He felt well for about six weeks after this operation. Around the middle of June, 1942, he again started to cough and around the first of July he had a chill followed by a fever, cough, loss of weight, poor appetite, and weakness. It was because of these symptoms that a diagnosis of tuberculosis was made by his physician and he was referred to the writer for an opinion.

Family History:
Irrelevant to the case, however, it is to be noted that there was no one in the immediate family with tuberculosis or asthma.

Physical Examination:
Patient was a well-built individual but poorly nourished and sickly looking. His temperature was 101°, pulse 90, respirations 22, weight 148 1/2, blood pressure 120/70.

Regional Examination:
Abnormal findings included the following: congestion of nasal and pharyngeal mucosa; teeth in poor condition; lips, mildly cyanotic. Expansion of the chest was limited on both sides, breathing was somewhat labored; there was dullness at the axillary region of both lungs and at upper half of right lung; medium rales were elicited on auscultation at the right base. The finger tips were slightly cyanotic.

Fluoroscopic Examination:
Revealed diminution of expansion in the upper half of right lung. Numerous calcified glands were seen in both hilar regions. The diaphragm moved freely.
Flat Roentgenogram (Fig. 1):

Brought by patient, taken on 7/7/42, revealed an inflammatory process peripherally located, involving the first and second interspaces on the right side, and the lateral third from apex to base of left lung. Roentgenogram taken on 7/26/42 (Fig. 2), reveals clearing of the lesion in the first and second interspace on the right side but extension to the base on the same side not seen in the film of 7/7/42. Likewise, on the left side of the infiltrations previously noted in the first interspace have disappeared. There has also been some clearing of the lower half of the same side. These films show the transient character of the inflammatory process characteristic of Loeffler's syndrome.

Laboratory Tests:

Sputum was negative for tubercle bacilli on direct smear and after concentration. Blood study revealed the white count to be 11,200; red count, 5,200,000; hemoglobin, 80%. Modified Arneth Schilling count was as follows:
Because of the history of nasal allergy, the transient character of the inflammation and particularly the eosinophilia (Fig. 3), a diagnosis of Loeffler's syndrome was made and patient was given symptomatic treatment based upon the supposition that the condition was an allergic pneumonitis. Specifically, he was given the following prescription—3 per cent ephedrine sulphate 10cc., saturated solution of potassium iodide 10 cc., and syrup of white pine to make a four ounce mixture; dose, one teaspoonful four times a day.

On September 4, 1942, the patient returned for re-examination. He stated that since his first examination by the writer, he had stayed in bed for over two weeks and that his temperature had dropped three days after the first examination. This time he had no complaints with the exception of weakness. His weight was 156½ lbs., temperature, pulse, and respirations were within normal limits. White count, 7800, red count, 6,620,000 hemoglobin, 90%.

Modified Arneth Schilling revealed:

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<th>Basophile</th>
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Fluoroscopy revealed complete clearing of the previous lesion. Flat roentgenogram taken on 9/4/42 (Fig. 4), showed complete clearing of the lesion. The patient has been under observation since his attack and has been seen frequently in the office, on June 6, 1944, last, mainly because of his difficulty in breathing which seems to have developed since his attack of Loeffler’s syndrome. His symptoms and physical signs, and present history, are those of a typical case of bronchial asthma. Since he states that an attack of dyspnoea and wheezing frequently follows a local treatment for his nasal condition, it is logical to assume that the patient may be allergic to the drugs used. Undoubtedly in this case the predisposing factor was an allergic background which prepared the soil for the development of the eosinophilic pneumonitis.

CONCLUSIONS

A review of the literature leads to the conclusion that Loeffler’s syndrome is usually found in individuals with an allergic tendency. Intestinal parasites are frequently found in association with Loeffler’s syndrome and may act as a contributory cause.

More recent investigations indicate that pathologically the condition represents an eosinophilic pneumonitis.
The outstanding findings in Loeffler's disease are the blood eosinophilia, the transient pulmonary infiltrations, the mild course, and the spontaneous healing without complications.

No specific treatment is known for the condition.

CONCLUSIONES

El repaso de la literatura nos conduce a la conclusión de que el síndrome de Loeffler generalmente aparece en individuos con tendencia alérgica. Con frecuencia se descubren parásitos intestinales en casos del síndrome de Loeffler y es posible que sean causa contribuyente.

Las investigaciones más recientes indican que, desde el punto de vista patológico, este síndrome representa una neumonitis eosínófila.

Los hallazgos principales de la enfermedad de Loeffler son: la eosinofilia en la sangre, las infiltraciones pulmonares transitorias, el curso leve y la curación espontánea sin complicaciones.

No se conoce ningún tratamiento específico para esta enfermedad.

REFERENCES

14 Wild, in Loeffler's discussion.


21 Wieland, E., in discussion of Loeffler. 1b


23 Lohr and Kindberg, quoted by Kartagener. 24


