

A SYNDROME OF GENERALIZED LYMPHADENITIS WITH NEUTROPHIL LEUCOPENIA.

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INTRODUCTION.

ON May 31, 1943, a soldier with a mass of glands in the right axilla was admitted to the Surgical Wards of a New Zealand Hospital in Tripolitania. Other glands were found enlarged, a provisional diagnosis of tuberculosis or Hodgkin's disease made and a biopsy was proposed but, after two to three days, the mass of glands had almost subsided and a further provisional diagnosis of infective mononucleosis was substituted though later a negative Paul-Bunnell test was found.

Five days after his admission two Medical Officers concerned in his care took ill with a febrile disease and later developed generalized lymphadenitis and neutrophil leucopenia.

It later became obvious that a mild epidemic of similar cases was occurring in the Sisters' Mess and among troops camped in the vicinity and that this disease was not typical infective mononucleosis.

This paper describes the findings in 25 selected cases whose records were most complete.

GENERAL DESCRIPTION.

In general, the syndrome is characterized by a short, usually mild bout of pyrexia which the victims describe as "like a mild sandfly fever." This is followed by a more or less generalized tender enlargement of lymph glands lasting five to fifteen days and a transient leucopenia, as low as 3,000 or less, chiefly affecting the neutrophil cells which may drop as low as 9 per cent (315 neutrophils).

Glands.—The glands varied greatly in size from that of an almond (1.5 to 2.5 cm.) to small shotty glands a millimetre or so in diameter. Most cases had at least one group of larger size. In some cases these larger glands appeared to be draining an area subject to recent sepsis such as "Desert Sores" or, in one Sister, furuncles of the aural meatus.

The consistency varied. The larger glands were soft and "fleshy." After a few days enlargement these would become suddenly smaller over a twenty-four hour period being transformed into smaller and firmer glands which might not have entirely disappeared when the patient was discharged.

The posterior cervical glands were usually the first to appear but, in a few cases, the inguinal group was the first noted. As previously stated sepsis seemed to determine both the size and early appearance of glands in some cases. Any or all of the superficial groups were involved in this enlargement, which was not necessarily symmetrical; one axillary group only might be involved. Both pre- and post-auricular glands, occipital glands and epitrochlear were commonly enlarged.

No particular predilection for side was noted but enlargement of cervical glands, deep to sternomastoids, and the supraclavicular group was invariable. In two cases vague abdominal pain was a presenting symptom, possibly due to enlarged abdominal glands.

The first patients in this series were Sisters or Medical Officers who endured the mild pyrexia without reporting sick and only reported when obvious glandular enlargement was

present. It was then thought that the gland enlargement followed some days after the pyrexia. However it later became obvious that most cases had enlargement on admission and, in a few cases studied from the onset, it appeared that there was slight glandular enlargement within forty-eight hours.

In most cases the generalized enlargement had disappeared within ten to fourteen days but the first group to appear was still often palpable. The spleen was palpable in only 3 of 25 cases.

Febrile Bout.—Most patients who had had sandfly fever described this as like a "mild sandfly infection." There was the same frontal headache with retro-ocular pain and mild aching in back and limbs. The average duration of pyrexia was five days with seven days as a maximum. Most cases had had one to two days pyrexia before admission. One case had a "relapse" with a fresh gland involvement commencing two days after the finish of the first bout and lasting two days. The pyrexia was rarely above 102° but occasionally reached 104°. In a number of cases the pyrexia was nocturnal only.

Other Symptoms.—Excessive lassitude or fatigue, with considerable difficulty in concentrating on work, was reported by many of the cases, especially the Sister-Medical Officer Group, who attempted to work through the attack.

A very constant feature was complaint of "stiff neck" which is believed to be analogous to that seen in infective mononucleosis and to be due to early inflammation of subjacent glands. This proved to be a most helpful early sign in "spotting" the disease. Two cases, a Medical Officer and a Sister, noted polyuria for twelve to twenty-four hours during the pyrexial bout. The significance of this is unknown and, though inquired for, was not seen in subsequent patients. Nevertheless it should be noted that ward temperatures were ranging from 85° to 120° and conditions were such as would explain all but the most pronounced polyuria.

Many cases showed a transient pharyngitis—an injection of mucosa only.

Rash.—One case only developed a rash on the eighth day lasting forty-eight hours. This was an ill-marked erythematous rash mainly confined to back and chest and showing no special characteristics.

Icterus.—Two cases were accompanied by icterus—apparently a coincidental infective hepatitis but mentioned here on account of recent reports of icterus with infective mononucleosis. One case was a N.Z. W.A.A.C., on the Hospital Staff, in whose Mess a small epidemic of infective hepatitis had occurred. Jaundice appeared four days after onset of pyrexia with a white cell count of 4,000 and a neutrophil count of 30 per cent. Generalized tender glandular enlargement appeared four days later. This patient was exposed to both infections. In the other case jaundice developed on the tenth day after admission for tender glandular enlargement with characteristic blood changes.

BLOOD PICTURE.

General Findings.—On the whole the characteristic features were the low white count, the absolute neutropenia and, in most cases, the appearance in increased numbers of an abnormal cell type. The figures for the total white count varied, usually dropping to about the 4,000 level, but in occasional cases remaining at a normal level throughout. There was an absolute decrease in neutrophils and, usually, only a relative increase in lymphocytes. At this time an abnormal type of cell appeared and for convenience was designated "atypical mononuclear."

Neutrophil Counts.—The neutrophils showed an absolute decrease, in all cases, shortly after the onset of symptoms, when the total white count usually commenced to drop until it again reached its normal level—usually round the 7,000 mark.

In this series of twenty-five typical cases blood examinations were carried out every few days. In only one case was the neutrophil count above 40 per cent of the total white count. In this case the figure recorded was 43 per cent—the white count being 3,900 per c.mm. The absolute figures for the neutrophils varied between 315 and 2,470 per c.mm.

The neutrophil count was below 45 per cent of the total white count for periods varying from one to eight days with an average of 3.8 days.

The following table gives an idea of the drop in neutrophils and the number of patients in each group. One case is omitted.

| <i>Total neutrophils per c.mm.</i> | | | | | | <i>No. of patients</i> |
|------------------------------------|-------------|----|----|----|----|------------------------|
| Under | 500 | .. | .. | .. | .. | 1 |
| | 500—1,000 | .. | .. | .. | .. | 3 |
| | 1,100—1,500 | .. | .. | .. | .. | 9 |
| | 1,600—2,000 | .. | .. | .. | .. | 6 |
| | 2,100—2,500 | .. | .. | .. | .. | 5 |

Normal figures (Whitby and Britton), were taken as follows:—

| | | | |
|--------------|-------|------------------|----------------|
| Total whites | 4,000 | 10,000 per c.mm. | |
| Neutrophils | 3,000 | 6,000 per c.mm. | 60—70 per cent |
| Lymphocytes | 1,500 | 2,700 per c.mm. | 25—30 per cent |

Two of the cases were interesting as illustrating varying features.

Patient "A" showed the characteristic drop in neutrophils, an absolute lymphocytosis and appearance of increased "atypical mononuclears," while the total white count remained normal.

Patient "B," a relapse case, showed a low white count at onset, a sudden return of neutrophils to normal, a further drop of neutrophils accompanied by "atypical mononuclears" and, again in this case, an absolute lymphocytosis. The counts illustrating the above are shown below:—

Patient "A"

| <i>Date</i> | <i>Total White Count</i> | <i>Neutro.</i> <i>%</i> | <i>Lym.</i> <i>%</i> | <i>Increased "Atypical"</i> <i>Mononuclears"</i> |
|-------------|--------------------------|----------------------------|-------------------------|---|
| 11.7.43 | 7,200 | 71 | 25 | — |
| 12.7.43 | 7,000 | 60 | 32 | — |
| 13.7.43 | 7,000 | 16 | 73 | + |
| 15.7.43 | 7,500 | 33 | 56.5 | + |

Patient "B"

| | | | | |
|---------|-------|----|----|---|
| 4.7.43 | 3,900 | 38 | 56 | — |
| 5.7.43 | 6,500 | 52 | 41 | — |
| 8.7.43 | 4,300 | 62 | 37 | — |
| 9.7.43 | 4,900 | 55 | 41 | — |
| 11.7.43 | 6,800 | 29 | 62 | + |
| 12.7.43 | 9,000 | 36 | 62 | + |

It must be admitted that a neutropenia may occur in malaria and other diseases, causing a leucopenia and, in one such case of B.T. malaria, a neutrophil count as low as 19 per cent (1,102 cells per c.mm.) was found but enlarged glands were not present.

Lymphocyte Counts.—In the majority of cases the lymphocytic increase was only relative and not absolute. When the white cell count dropped to about 4,000 per c.mm. and was accompanied by this relative increase in lymphocytes it was noticed that there was an increase in the abnormal type of cell resembling, but differing in some aspects from, the Türk Irritation Cell.

Such cells have been noticed in very small numbers, prior to this outbreak, in blood films showing a decreased white cell count accompanied by a relative lymphocytic increase, a finding later confirmed in such cases, particularly in some positive malarial films.

The numbers of such cells were usually in the neighbourhood of $\frac{1}{2}$ per cent or less of the differential count. In the films of the glandular cases the increase was more noticeable being in the neighbourhood of 2 to 3 per cent. Such cells appeared either when the white count was at its lowest figure or, more often, when the count commenced to rise again—the relative lymphocytosis being most marked about this time, usually 60 to 70 per cent.

That this increase in abnormal cells was fairly characteristic of this form of glandular disease was shown in one case when a newly admitted patient with P.U.O. had a routine blood film examined for malaria and showed a 3 per cent figure of these abnormal cells. Subsequent examination of the patient proved that he was an example of this syndrome.

The cell in question, although varying slightly in size, is intermediate between the small and large lymphocyte with usually an eccentrically-placed nucleus. It has very deep blue staining cytoplasm, evenly granular in appearance, and a round or oval-shaped nucleus, also very deep staining, so deep usually that it is hard to differentiate nucleus and cytoplasm (Leishman stain) except by the difference in colour between the deep blue of the cytoplasm and deep violet of the nucleus.

Except for this very deep staining nucleus it resembles the Türk Irritation Cell and may possibly be just a variant of this cell. The nucleus is usually too deeply staining to allow of its structure being seen in detail but appears to be reticular in type. No evidence of vacuolation in the cytoplasm was observed in any of these cell types nor were azure granules present.

Cell types intermediate between the normal lymphocyte and this cell were noticed before the total white count reached its lowest point and during its rise to normal figures again.

These "intermediate" cells, on the whole, were slightly larger in size and more closely resembling the Türk Cell, with paler, evenly staining nucleus and a less granular but evenly staining deep-blue cytoplasm which, on occasions, contained clear unstained vacuoles.

The appearance in increased numbers and disappearance of the abnormal deeply staining type, or "atypical mononuclear," was usually quite sudden, appearing and disappearing in a day or so—very seldom remaining beyond a maximum of three days.

A few cases failed to show any of these typical types during the course of the illness but, otherwise, showed the usual features.

Brigadier L. E. H. Whitby, who examined some of the "atypical" cells, would not commit himself beyond saying that they were obviously abnormal types.

Other Leucocytes.—There was no variation of other cell types in all the cases examined. The monocytes were not increased in any of the cases and showed no abnormality.

Sternal Puncture.—This was carried out on two of the typical cases with inconclusive results.

Paul-Bunnell Test.—Agglutination tests were carried out in ten cases against suspensions of sheeps' corpuscles. All, however, gave normal results. Two other cases, not included in the present series, also gave normal results (i.e. negative tests). These tests were performed on two groups of patients and included some of the earliest and some of the latest cases in the series. In seven the tests were performed between the tenth and twentieth days, two being repeated after forty-five days. In the other three the tests were performed thirty-five days after the onset.

EPIDEMIOLOGY.

The mode of spread is quite unknown. In a community subject to a mild epidemic it is unsafe to guess at an incubation period. The following facts may be stated for future consideration. Following the admission of the first (probable) case two Medical Officers, who saw him, developed fever five days later followed by the typical syndrome. One of these officers went away for a week-end during the pyrexial period and, seven days later, two of his companions—Medical Officers of a neighbouring unit—took ill with similar symptoms. There was, however, considerable interchange of visits between the units.

In an Officers' Mess, numbering about 25, 5 officers and the Mess Corporal were taken ill. The two first cases were admitted to hospital on June 11 and 12. A further case appeared on June 20 and three cases on June 23, 25 and 27.

It is possible, therefore, that the incubation period may prove to be about seven days.

GEOGRAPHICAL DISTRIBUTION.

All except three of these cases had been encamped within a radius of 15 miles of Tripoli on admission. Of the remaining three, two were evacuated from Sicily, having previously

been in Tunis and Sfax. The third was also evacuated from Sicily just after his arrival from Tripoli and he stated he was not well when he left this area.

In addition, it is noted that other hospitals in the Middle East have reported "atypical" cases of so-called "glandular fever." (Quarterly Report, Consultant in Tropical Med., M.E.F., September 19, 1943.)

The blood-count was stated to be "normal" in one series but, in view of the transitory nature of the neutrophil leucopenia, this feature may have been missed.

NATURE OF SYNDROME.

The causative organism is unknown. A biopsy of a lymph gland has not been done in the present series.

Owing to the exigencies of the Service no access to literature is possible at present and it is not known if similar cases have been reported in the past.

The salient features of the cases described were a febrile attack associated with general glandular enlargement followed, after a two to seven day interval, by a reduction in circulating neutrophils.

In the course of the "epidemic," however, two or three cases out of forty were seen, clinically typical but without the marked drop in neutrophils. In two of these it seemed unlikely that such a drop could have been missed if it had occurred.

Though there is a superficial clinical resemblance, it is obvious these are not cases of Infective Mononucleosis. The blood counts are consistently different and the Paul-Bunnell test negative in all cases on which it has been performed.

The combination of lymph glandular enlargement and neutrophil leucopenia occurs in many diseases of viral causation, from rubella to the sandfly-dengue group. It is quite obvious that these cases were not in the exanthem group nor did they show the features of Mosquito Dengue.

One of the authors (J. D. C.) saw a series of cases, in the autumn of 1940, in troops who had recently come from Palestine to Egypt. These cases were called "sandfly fever," but had glandular enlargements somewhat resembling those in the present case—blood counts were not done. No sandfly fever epidemic has occurred in this area during the period under discussion and only a few sporadic cases resembling sandfly fever have been admitted to this hospital. Nevertheless it would appear possible that these cases were somewhat unusual types of sandfly (phlebotomus) fever or due to an unknown virus of the sandfly-dengue group.

On the other hand, cases of "atypical" glandular fever with negative Paul-Bunnell tests are reported to have occurred in England (personal communications) and the present cases may belong to a geographically widespread group related to infective mononucleosis.

SUMMARY.

(1) Twenty-five cases showing febrile glandular enlargement, a neutrophil leucopenia and a negative Paul-Bunnell test are reported. These cases were selected from more than forty cases appearing in a small epidemic between May 31, 1943, and August 11, 1943.

(2) The circulating neutrophils were under 2,500 per c.mm. in all cases and varied from 315 per c.mm. to 2,470 per c.mm.

(3) An atypical cell, somewhat resembling a Türk Irritation Cell is described. The number of these cells present reached 2 to 3 per cent of total white count. Occasional cells of this type have been seen in other cases with low neutrophil counts; e.g. malaria.

(4) The causative organism is unknown. It is suggested it may be a virus related to either that of infective mononucleosis or the sandfly-dengue group.

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