Part VII.—Monocytic reaction in myelosis

BY

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AND

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We have recently recorded a case of monocytic leukæmia in a child in which autopsy and histological examination revealed a generalized reticuloendotheliosis.

The case here recorded is one in which the blood picture for a period of nearly six months showed a leucocytosis with marked increase in the number of circulating monocytes, and together with the clinical findings made monocytic leukæmia the most probable diagnosis. Unfortunately for the four months immediately preceding her death the child was not seen. A post-mortem examination obtained by the help of Dr. Dingley and Dr. Morris, of Wednesbury, revealed no evidence of the previous monocytosis, and showed that death had been due to myelogenous leukæmia.

Case report.

I. C., female, was born in October, 1930. She was the fifth child, three of the others being alive and one having died of gastro-enteritis. Born at term, she weighed 8 lb. She was never breast fed, and was reared on Cow and Gate food. At the age of 10 months, when the weight was 17 lb., her mother observed that the child’s abdomen was enlarging. She was observed to have bruising of the arms and legs and face and subconjunctival haemorrhages; her tonsils were enlarged and she was anæmic. The liver and spleen were enlarged. No other abnormal physical signs were noted. She improved considerably with general treatment, but 2 months later, at the age of 12 months, she began to show a rise of temperature and was admitted to the Birmingham Children’s Hospital.

On admission the child looked ill and slightly anæmic. She was of average build and weight, and had no elevation of temperature. There was no jaundice. The heart and lungs showed no abnormality. Her liver was enlarged and smooth, and her spleen greatly enlarged, extending down to the left anterior superior spine, and quite smooth. The glands of the neck, axillæ and groins were all slightly enlarged, discrete and not adherent to surrounding tissues. There was no rickets. Beyond a few small and fading ecchymoses on the legs, there were no signs of purpura. The mother’s Wassermann reaction was negative, and the child showed a negative Mantoux reaction.

The condition of her blood on admission is shown in the table. Bleeding time, clotting time and fragility of the red cells were normal.

A week after admission the child developed a transient gastro-enteritis with marked dehydration. At the same time her spleen was much reduced in size, and in the peripheral blood an increase in the number of white cells was noted. This latter phenomenon was interpreted as being due, at any rate in part, to the outpouring of cells from storage in the spleen in response to its contraction. She recovered from this attack and her blood picture, apart from the leucocytes, improved and remained fairly steady. The spleen increased again in size, though not to its former extent,
She was kept in hospital for 4 months, during which time 14 blood examinations were made; 7 of these at approximately monthly intervals are set forth in the table. Her weight chart showed a steady gain, her colour, temper and appearance soon became those of a healthy infant; but the white cell count remained raised, and the monocytes ranged always from about 20 to 40 per cent. of the leucocytes. The spleen, while varying from week to week, was always much enlarged, and the liver remained enlarged throughout. X-ray examination of her bones revealed no abnormality. Apart from one ecchymosis on the forehead, no signs of purpura were observed.

The diagnosis was regarded as probably one of monocytic leukaemia, but as her condition was so good after 4 months in hospital she was allowed to go home.

She attended the out-patient department for two months and for this period continued to be in good condition. Her last blood count, two months after leaving hospital, showed a fall in the haemoglobin and red cells, and re-admission was suggested. Unfortunately the parents transferred the child to the care of a welfare centre, and she was not seen again alive by us. She died four months later.

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Reference to the Table will show that for nearly 6 months (October, 1931, to April, 1932), the white cell count was raised to between 15,900 and 81,000 per c.mm. The erythrocyte counts were normal until the last few blood examinations, in which a tendency to fall is noted, particularly in the last count of April 19th, 1932. The haemoglobin during the period under observation varied between 52 and 70 per cent. In other words, beyond showing a slight hypochromic anaemia at times, the erythron was not affected except at the time of the last count. The reticulocyte counts indicated a normal, or at times slightly over-active, red-cell marrow. Except in the first count, the platelets were always below normal in number.

Apart from the constant and varying degree of leucocytosis, two points stand out in the differential distribution of the white cells; first, the high percentage of typical monocytes; and secondly the tendency towards immaturity of the myeloid cells, as shown by the constant appearance of young forms in numbers slightly greater than normal. The lobulation of the mature polymorphonuclear cells was also suggestive of immaturity, and it was unusual to find more than one or two cells with more than two lobes,
The appearance of the various white cells was carefully watched. Immature lymphocytic cells were not seen. The immature myeloid cells were quite typical. The monocytes were of mature type and presented in themselves no abnormality; the nuclei were oval or kidney-shaped, the nucleoplasm staining in the typical streaky way with Leishman's stain. The cytoplasm was of the bluish opalescent type, some of the cells having fine pink cytoplasmic granules. Pseudopodia were not present, and there was no resemblance to the histiocyte. The oxydase reaction was negative.

On first seeing the child the diagnosis on clinical grounds of von Jaksch's anaemia suggested itself. The blood examinations, when added to the clinical findings, indicated two possibilities, infective mononucleosis or monocytic leukaemia. After following the case, however, for six months with little if any change for the worse on the one hand or improvement on the other, the tendency was to distrust either diagnosis.

**Fig. 1.**

Composite drawing of monocytes; mature lymphocytes are also shown.

What occurred in the blood between her last examination and her death must remain a mystery, but the histological examination of the tissues throws some light on this problem.

**Autopsy.**—Body of a moderately nourished pale child showing many scattered fine petechiae.

**Thorax.**—Thymus was slightly large. Lungs showed terminal broncho-pneumonia, especially in the lower lobes. Mediastinal glands were grossly and uniformly enlarged, rather red-pink in colour. Pericardium showed a few petechiae, and contained a few drachms of straw colour fluid. Heart was pale, flabby, and showed a few petechial haemorrhages.
ABDOMEN.—Peritoneal cavity contained a small quantity of free fluid. The liver was considerably and uniformly enlarged, and showed on section a fine thickening of the portal tracts, rather similar to an early interlobular cirrhosis; no deposits; some fatty degeneration. The spleen was grossly enlarged and extended almost to the pelvic brim; no deposits, surface smooth. The kidneys were pale. The mesenteric glands were moderately enlarged, fairly soft and pink. In the inguinal and lumbar regions were scattered moderately enlarged lymph glands. No abnormality was noted in the other organs.

PHARYNX.—Both tonsils were much enlarged and presented a somewhat fungating, red smooth and lobulated surface towards the midline.

BONE MARROW.—In the femur (shaft) the bone marrow was copious, pink and cellular.

Histological examination.—Tissues were placed in formalin approximately 36 hours p.m. (August), and sections were stained with haematoxylin and eosin.

BONE MARROW.—The low power showed the marrow to be unusually cellular, though red cells were extremely scanty; the white cells were of various shapes with round forms prepondering. Under the high power a large number of myeloblasts were found: these cells had round or slightly oval nuclei, with well defined nuclear membrane and one or more nucleoli; their average size was 8µ. Myelocytes and metamyelocytes with kidney-shaped nuclei were numerous. Though their nuclear shape was similar to that of monocytes, they were smaller; their structure was of the same nature as the other cells of the granular series. Very few mature polymorphonuclear cells were to be seen. Eosinophil cells, immature and mature, were numerous. A fair number of small darkly staining round cells were scattered amongst the myeloblasts. These showed scarcely any cytoplasm. The nuclei stained more deeply than those of the lymphocytes in the lymph glands. It is probable that these dark cells were normoblasts, the cytoplasm of which had been lysed on account of the delay of 36 hours before autopsy. Reticular cells were to be made out in small numbers; they appeared normal. In brief the marrow represented an advanced myelosis. There was marked immaturity of the myeloid series, but erythropoiesis was present.

LIVER.—There was a moderate infiltration of the portal tracts with small round cells with a few myeloid cells which shewed the appearance of myeloblasts. Though the sections were taken 36 hours after death, the cells stained well and there was little degeneration of the central hepatic cells: myeloblasts, myelocytes, metamyelocytes and polymorphonuclear cells were found in the sinusoids. No areas of metaplasia were seen. Mitoses were not found. The Kupffer cells were normal.

LYMPH GLANDS.—Under the low power the lymph follicles were somewhat difficult to make out owing to the large number of white cells in the pulp. There was some congestion of the blood vessels, which shewed a greatly increased proportion of white cells in their lumina. In the pulp were scattered small clumps of larger, round and more deeply staining cells, which under higher magnification proved to be myeloblasts. Under the high power the centres of the lymph follicles and the pulp shewed slight increase in reticular fibres. Myeloblasts were found mingled with lymphocytes on the outskirts of the lymph follicles. The lymph sinuses contained many myeloblasts. Throughout the pulp was a good proportion of lymphocytes with plentiful small clumps of myeloblasts and practically no red cells. The monocytes, present in the high proportion of 30 per cent. in the peripheral blood 4 months before death, did not appear to be present, since but few large lightly staining cells were to be found. Reticular cells were distinguishable, and apart from slight increase in number and in amount of fibrous processes, were normal in appearance. Fine granules of brownish pigment of hematoïdin were scattered in the reticular network.

SPLEEN.—As in the lymph glands, the lymph cords were relatively indistinct owing to the cellularity of the pulp. Fibrous tissue was slightly increased. The endothelial
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Fig. 2.
Microphotograph of monocytes. An immature metamyelocyte (Me) and basophil (Ba) are also shown (x 820: Leishman).

Fig. 3.
Microphotograph of monocyte and a myelocyte (x 725: Leishman).

Fig. 4.
Microphotograph of marrow, showing myeloblasts and some normoblast nuclei (x 725: H.E.)

Fig. 5.
Microphotograph of liver, showing myeloid cells in sinusoids; Kupffer cells normal or somewhat smaller (x 400: overstained H.E.)
tissue in the centres of the lymph follicles was slightly proliferated and amongst them a few cells of monocyte type were seen. The cytoplasmic processes of these were not visible probably owing to post-mortem change, but the nuclei were about 9μ in the longest diameter, and of kidney shape; the size of these cells was therefore considerably greater than that of the myeloblasts.

The most striking cells in the pulp were myeloblasts which were aggregated here and there into small clumps of half a dozen or more, and most were approximately 8 to 10μ in diameter. More mature cells of the granular series were fairly numerous. Here and there a very few more lightly staining cells with kidney-shaped nuclei were to be made out; these were possibly monocytes, but their number was extremely small. A number of eosinophil cells, generally younger than polymorphonuclears, was present.

There was a general increase in the fibres and cells of the reticulum; a few of the nuclei of the reticulo-endothelial cells were somewhat swollen, and their processes blunter and stouter. The increase in reticular fibres tended to vary in amount.

Another section examined showed in one area cellular proliferation of the endothelium with myeloblasts present in it. Some of these myeloblasts appeared to have blunt processes and to be only partially free. In other respects they were similar to the free myeloblasts. It thus appeared that there was some myeloid metaplasia in the pulp of the spleen. Red cells were almost absent. No giant cells were found.

KIDNEY.—The glomeruli appeared more cellular than normal, but myeloblasts were not detected in their capillaries. Capsules were normal. The convoluted and spiral tubule cells were pigmented and cloudy in appearance, and the nuclei stained faintly; these changes were in large part due to post-mortem autolysis. Most of the cytoplasm of the other tubules was missing, so that nuclei appeared numerous, no leukemic infiltration was discovered.
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LUNG.—There were marked bronchial catarrh and desquamation of epithelium. Areas of collapse and compensatory emphysema were numerous. There were also areas of pneumonia where the alveoli contained many macrophages, laden with greenish-gold pigment, desquamated epithelial cells and young neutrophil leucocytes. The arterioles contained many similar neutrophils and some myeloblasts, and surrounding the vessels were small leukæmic infiltrations of myeloblasts. A few somewhat larger areas were composed entirely of round myeloblasts, packed so densely, that it appeared that myeloid metaplasia was present. Search, however, failed to reveal mitoses. A similar area was found in the adventitia of an arteriole. The vessels were congested. Most of the contained myeloblasts measured 8 or 9μ; but some were smaller, and the mature polymorphonuclear cells measured about 7μ.

OTHER ORGANS.—The intestine showed but little abnormality. One or two myeloblasts were found in the intestinal tissue. Post-mortem autolysis was considerable, and the epithelial layer was missing. The ovaries were normal, except that blood in the vessels showed a great increase in white cells. The uterus was normal. In the suprarenal bodies, the cortex was normal, with some toxic degeneration of cells. Cells of the medulla were diminished, a few were to be found lying in areolar tissue and containing a good amount of yellow pigment. There was no leukæmic infiltration. In the thymus, the medulla showed a little increase in the reticular tissue, and Hassall’s corpuscles were slightly diminished in number. Lymphocytes were numerous in the medulla. No leukæmic infiltrations were found. The myocardium showed slight infiltration of myelocytes and metamyelocytes between the fibres. Muscle fibres were well striated.

Discussion.

It is seen from the report of this case that though there was room for speculation during life as to the correct diagnosis, the histological investigations yielded a picture typical of myelosis: yet the last blood count examination, four months before death, revealed only slight evidence of immaturity of the myeloid elements, though the proportion of monocytes was still high (85 per cent.). No increase of monocytes was found anywhere in the tissues, and so no light is thrown on the origin of these cells.

The characteristic picture of monocyotic leukæmia shows (a) an increase in the peripheral blood of monocytes or histiocytes (large cells showing pseudopodia, prominent fine granulation, and nuclear complexity and negative oxydase reaction); and (b) a cellular proliferation of reticulo-endothelial cells of the organs containing this tissue; accompanying the proliferation is a widespread infiltration with cells of monocytic characters: large (15 to 40μ), bulky, pale basophilic cytoplasm, with oval, indented or lobulated streaked nuclei. Against this cellular hyperplasia of the reticulo-endothelium, is its reaction in the spleen and lymph glands in myelosis; here is often seen a more reticular type of proliferation, suggesting an irritative reaction. Moreover, as in this case so also in myelosis, cellular areas of myeloid metaplasia may be found: but interspersed with the swollen reticulo-endothelial cells will be found cells of myeloblastic character, which are distinguishable from those of histiocytes and monocytes.

In the peripheral blood picture of the present case the monocytes were entirely normal in appearance, whereas in our case of monocyotic leukæmia1 recorded elsewhere, they showed pseudopodia, excessive granularity of the cytoplasm, and nuclear complexity—characters regarded as histiocytic by
many. Examination of the white cells present in blood vessels of the tissues showed a great increase in myeloid cells, scarcely any of which appeared to be monocytes. The previous high monocytosis had disappeared at the time of death.

Elsewhere we have referred to the interesting question of the origin of the monocyte, and have suggested that the reticulo-endothelium of lymph glands takes a large share in their production. It is possible that in the present case, the chronicity of the myelosis provided a prolonged stimulus to the lymphatic tissues, thus causing an outpouring of monocytes. Chronic leukæmas are uncommon in children, whose lymphatic systems react strongly; were they more common it is possible that this monocytosis would be found more frequently.

**Previous cases.**—We have traced the records of several somewhat similar cases in older patients.

Merklen and Wolf²,³ have recorded two such interesting cases. Among several others was that of a workman who had the symptoms of acute leukæmia, with ulceration in the mouth, fever, and enlargement of liver, spleen and lymph glands. On admission myeloblasts accounted for 68 and monoblasts and monocytes for 23 per cent. of 200,000 white cells, with similar proportions the day before death. There were multiple leukæmas of the skin and lungs. Histologically, there was myeloid proliferation of the bone marrow, and infiltration of the liver and spleen with large monocyteid cells. There was also hyperplasia of glandular reticulum.

In their other case the spleen was not palpable, and a clinical diagnosis of atypical myeloid or monocyteid leukæmia was made. The white cell count was 28,000, with myeloblasts 28·5, monocytes 24, monocyteid cells with very lobulated light nuclei 9, monoblasts 22·8 per cent.; eosinophil cells also were present. This patient improved after X-ray treatment and, in view of the present case, it is interesting to note that fifteen months after the first count the monocytes had practically disappeared, but a high proportion of myelocytes and myeloblasts remained.

Craciuneanu and Calalb⁴ have described a case of myelogenous leukæmia with enlargement of the lymphatic glands, in which mononuclear elements, which they regarded as monocytes, appeared in the final stages of the illness. Unfortunately they did not describe these cells in detail nor publish illustrations, and it is quite possible that these were myeloblasts, though no doubt their general appearance resembled that of monocytes.

Monocyteid features in myelosis were shown in the cases of Alder⁵, Naegeli⁶, Ewald, Frehse and Hennig⁷, Bykowa⁸, Hittmair⁹, and Schwarz¹⁰. In some of these the cells were rather monocyteid myeloblasts than true monocytes.

**Differential diagnosis.**—It therefore may be accepted that rarely a monocytosis occurs in the course of myelosis, and that in the presence of monocytosis the possibility of underlying myelosis should be borne in mind. At present, it appears impossible to define the characters of the clinical and blood pictures so adequately as to enable a diagnosis to be made with certainty. The other cases quoted showed a marked immaturity of the granulocytes, with definite myeloid leukæmic cells present; but that this immaturity of myeloid elements cannot be relied upon always to reveal itself, is proved by our present case, which showed typical monocytes in large numbers. It is probable that any case of monocytic leukæmia would reveal immature forms of monocytes or histiocytes in the peripheral blood.
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Diagnosis from an infective mononucleosis should be easier as that condition, though glandular enlargement is present, shows little diminution in haemoglobin content and red cell count, great depression of the granulocytes both absolutely and relatively, with little or no immaturity; hepatic and splenic enlargements are not pronounced; above all, there is not the clinical deterioration.

Conditions such as malaria and kala azar show less marked monocytic reactions, and other features which should prevent confusion with a leukaemic process. Agranulocytic angina shows necrosis of the pharynx, and a blood picture almost lacking in any myeloid elements and usually without a monocytosis.

Reference to the records has revealed that most authentic cases of monocytic leukaemia or leukaemic reticulo-endotheliosis show almost an entire absence of eosinophil cells from the peripheral blood stream (Ugriumow, Boch and Wiede, Hittmair, Hannema); whereas, as is well known, these cells are common in myelosis. The eosinophil count may therefore be an indication; in the present case it points against monocytic leukaemia.

The following conditions have been recorded as showing monocytosis of leukaemic or aleukæmic type:

1. Monocytic (or histiocytic) leukaemia (Clough).
2. Leukaemic reticulo-endotheliosis (Boch and Wiede, Gittins and Hawksley). Both of these are rare conditions.
3. Monocytic reactions in myelosis (Merklen and Wolf).
4. Monocytoid cells regarded as types of myeloblasts in myelosis (Hittmair).

Further, some cases have recently been described, mainly by German workers, in which there is usually no monocytosis in the blood stream, but which show limited or widespread reticulo-endothelial hyperplasia of a cellular type, and are possibly due to infective processes (Tschistowitsch and Bykowa, Akiba). The relationship of these conditions is discussed above.

Our present case falls under the third heading of the above list.

Summary.

A case of prolonged monocytosis in a child, shown at autopsy to be incidental in the course of a chronic myelosis, is recorded.

Brief reference is made to similar conditions and their relation to monocytic and histiocytic leukaemia and leukaemic reticulo-endotheliosis is discussed.

REFERENCES.


