Virchows Arch. A Path. Anat. and Histol. 368, 243—251 (1975)

Pathoanatomical Features of the Kidney in Myelomonocytic and Chronic Lymphocytic Leukemia

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Received June 18, 1975

Summary. The kidneys of 18 autopsy cases of myelomonocytic leukemia (MML) were examined for MML-specific features. Nine cases of chronic lymphocytic leukemia (CLL) served as controls.

The kidneys of the cases of MML showed macroscopically detectable sings of hemorrhagic diathesis and secondary uric acid diathesis more often than those of CLL. In the MML group most of the kidneys weighed more than the normal average for the corresponding age group, but the average renal weights for the 2 groups were about the same. Renal weight and grade of leukemic infiltration, particularly in MML, revealed no significant positive correlation.

In most of the cases of MML there were unevenly distributed poorly defined leukemic, infiltrates in the renal cortex and medulla. The histology resembled that of pyelonephritis. In CLL, on the other hand, the leukemic infiltrates were usually sharply defined and localized in foci in the outer cortex and the corticomedullary border region.

Renal dysfunction in cases of MML has been attributed by others to hyperlysozymemia. It was found occasionally but there was no MML-typical morphological substrate in our material. Hyaline droplet change of the tubular epithelium was more frequent and more pronounced in MML than in CLL. However, we also determined that it was nonspecific and that it was not a parameter of cell damage. Tubular hyaline droplet change and the morphological criteria of acute renal failure were not positively correlated with the degree of leukemic infiltration of the kidneys or with the leukemic proliferation as a whole. Instead, they were considered to be signs and symptoms of accompanying or secondary diseases which complicated the leukemia.

Key words: Kidney — Myelomonocytic Leukemia — Chronic Lymphocytic Leukemia — Weights of Kidney, Liver, and Spleen and Leukemic Infiltration — Hyperlysozymemia — Hyaline Droplet Change — Pathoanatomical Features.

Renal failure which is directly related to a leukemic infiltration of the kidney has been observed only in some cases of leukemia and malignant lymphoma. In most of these cases renal dysfunction manifested in azotemia shortly before death (Richmond *et al.*, 1962; Zollinger, 1966; Bohle, 1970; Ellman *et al.*, 1974). Usually the most common causes of secondary renal failure, which are not dependent on a particular type of leukemia, are obstructive nephropathy, pyelonephritis or interstitial nephritis, uric acid diathesis, and derangements in the mineral balance (Norris and Wiener, 1961; Zollinger, 1966; Ballard and Marcus, 1970; Haskell *et al.*, 1971; Palva and Salokannel, 1972; Greul and Lozano-Tonkin, 1974).

Pruzanski and Platts (1970) assumed that the disturbances in glomerular and tubular function observed in patients suffering from acute monocytic or myelomonocytic leukemia are due to hyperlysozymemia. Osserman and Azar (1969) described tubular droplets and distortion of mitochondria and nuclei, apparently caused by reabsorbed lysozyme. The highest serum and urine lysozyme

values are found in monocytic leukemia and MML, whereas the blood values in CLL are normal or even subnormal (Finch *et al.*, 1964; Osserman and Lawlor, 1966; Noble and Fudenberg, 1967; Catovsky *et al.*, 1971; Tischendorf *et al.*, 1972).

We looked in our hematological autopsy material for typical and possibly lysozyme-dependent renal lesions in cases of myelomonocytic leukemia (MML). Cases of MML were compared with cases of chronic lymphocytic leukemia (CLL). The diagnosis of MML or CLL was made from the autopsy material on the basis of cytological and histological criteria. In some cases the results of histological examinations of biopsy material were also available. The pathoanatomical diagnosis agreed with the clinical diagnosis in most cases.

Material and Methods

Eighteen autopsy cases of MML in adults, 39 to 85 years old. Nine cases of CLL with approximately the same age and sex distribution.

Fixation and Staining. 4–6 μm sections were prepared from material that had been fixed in Formalin and embedded in paraffin. The sections were stained according to the following methods: hematoxylin and eosin, scarlet or oil red, PAS reaction, Giemsa, Goldner, Ladewig, and Gomori. Slides of MML were also subjected to the naphthol-AS-D-chloroacetate esterase reaction (Leder, 1964).

The degree of leukemic infiltration in all organs was examined histologically and classified as follows: 1) absent or inconvincing infiltration, 2) low-grade infiltration, i.e. single foci of involvement, 3) moderate infiltration, i.e. large foci or disseminated small foci of infiltrates, 4) massive infiltration, i.e. diffuse or disseminated large foci of infiltrates.

In all cases of MML the degree and extent of the leukemic infiltration were determined in the bone marrow, the liver, and the spleen. The percentage of monocytic proliferation in these organs was estimated. A gross examination of the femoral bone marrow served as a parameter for the leukemic proliferation.

Results

Gross Examination

In 3 cases of MML gray-white nodules on the renal surface indicated leukemic infiltration. Six out of the 18 cases of MML and one out of the 9 cases of CLL revealed parenchymal and pelvic bleeding. Three cases of MML showed so-called uric acid infarcts as well as uric acid concrements in the lower urinary tract.

The weights of both the kidneys from the group with MML and those from the group with CLL were higher than the average for the corresponding age group of normal individuals determined by Roessle and Roulet (1932).

Enlarged kidneys were moderately to massively infiltrated in the majority of the cases of MML and in approximately half of the cases of CLL. However, the kidney weight and the degree of the histologically defined leukemic infiltration showed no significant positive correlation.

The same discrepancy in organ weight and degree of leukemic infiltration was also found in the liver. As depicted in Table 1, strongly infiltrated livers in cases of MML revealed only moderate enlargement. Hepatic involvement of a high degree could even be associated with a subnormal weight. On the other hand, moderately and highly enlarged spleens in MML always showed massive and usually diffuse leukemic infiltration.

Table 1. Weights of the kidneys, liver, and spleen compared with the degree of leukemic infiltration and the macroscopically determined amount of neoplastic femoral bone marrow with respect to the whole length of the femur in 17 autopsy cases of MML

Case	Age	Sex	Kidneys		Liver		Spleen		Femur Neoplastic marrow
			Weight g	Leukemic infiltration	Weight g	Leukemic infiltration	Weight g	Leukemic infiltration	
1.	39	m	410	+/++	1895	+	265	+++	1/1
2.	47	f	620	++	2740	+	260	+++	no data
3.	54	m	350	+	1880	++	110	++/++	+2/3
4.	59	f	280	+/++	1250	+++	590	+++	1/1
5.	60	m	300	++	1700	+/++	490	+++	1/1
6.	61	f	240	+	1835	++	450	+++	2/3
7.	62	m	510	+	1820	+	320	++	1/2
8.	64	m	430	+/++	2960	++	950	++	1/1
9.*	66	m	340	+/++	2400	+/++	640	+++	no data
10.	68	f	590	++/+++	2850	+/++	490	+++	patchy
11.	68	m	385	+++	1970	+	270	++	1/1
12.**	68	m	280	+/++	2250	+	850	+++	1/1
13.	71	f	230	+	1120	+/++	240	++	2/3
14.	71	f	270	+	1150	+	100	++	2/3
15.	74	m	350	++	1750	++	185	+++	1/1
16.	75	m	250	+	1830	+	340	+++	2/3
17.	85	f	no data	+	1250	+	130	+/++	1/1

+ = inconvincing or low-grade, ++ = moderate, +++ = massive.

* Osteomyelosclerosis with transition into myelomonocytic, terminally immature myeloblastic leukemia.

** Mast cell reticulosis and mature myelomonocytic leukemia.

Microscopic Examination

Leukemic Infiltration. 17 out of the 18 cases of MML disclosed renal involvement, 2 of a massive, 9 of a moderate, and 6 of a low degree. There was leukemic infiltration in 8 out of the 9 cases of CLL, in 5 of a moderate, in 3 of a low degree. The cytological features of the leukemic infiltrates in the kidneys resembled those of the infiltrates in the bone marrow.

In both types of leukemia the main localizations of the infiltration were the cortex and the border region between the cortex and medulla, here particularly the perivenous areas. The pattern of distribution of the infiltrates was sometimes the same. However, the majority of the cases of MML revealed infiltrates in the cortex and the outer medullary area. This pattern of infiltration histlogically resembled that of pyelonephritis (Fig. 1). On the other hand, CLL infiltrates were found in quite sharply defined foci in the outer cortex and at the corticomedullary border (Fig. 2).

When there was loose diffuse leukemic infiltration, the interstitial fiber network appeared stretched (rope-ladder-like picture). The usually delicate alveolar fiber network remained intact in MML even in large focal infiltrates. In CLL the often coarse fiber network was frequently found in spur-like pieces. Particularly

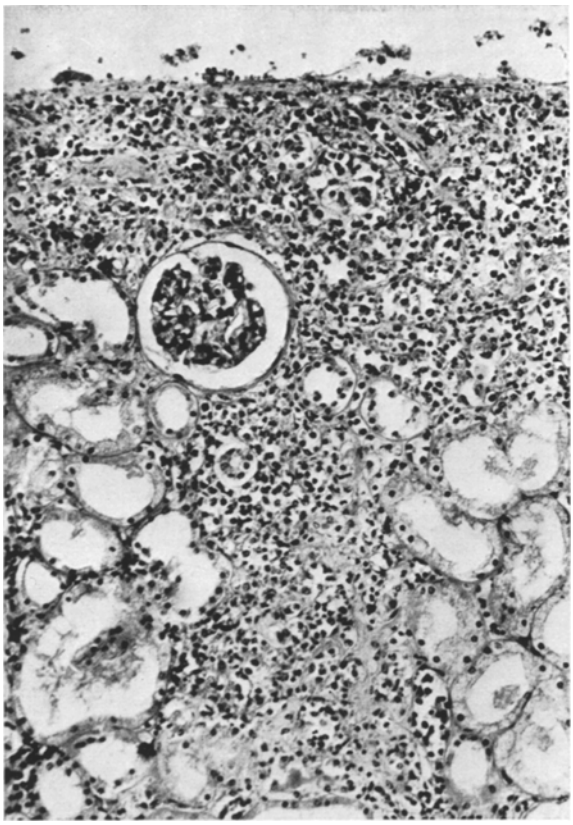

Fig. 1. Striated leukemic infiltrate in the outer cortex of the kidney. The glomerulus is intact. MML with a high percentage of monocytes. Male, 68 years old. H & E. × 140

in one case of CLL with tumor formation, the infiltrates sometimes showed a pseudofollicular structure (Fig. 3).

Glomerular lesions caused by local leukemic infiltrates were less severe than tubular lesions. Intact glomeruli were surrounded by large and cell-rich leukemic infiltrates (Fig. 1). Occasionally however, compressive lesions similar to those found in pyelonephritis could also be seen in the infiltrated cortex (Fig. 4).

Tubular Lesions. Tubules within leukemic infiltrates were often atrophic (Fig. 1). However, unaltered tubules were also seen, unrelated to the extent and cell density of the infiltration. In kidneys of both groups showing features of acute renal failure, the tubules could be widened even within cell-rich infiltrates. Hyaline droplet change (h.d.ch.) was found in the epithelium of the proximal tubules with approximately equal frequency in both groups, i.e. in 7 out of the 18 cases of MML and in 3 out of the 9 cases of CLL. However, it was more pronounced in the cases of MML. In both MML and CLL it was mainly focal, but in MML it affected some or many nephrons to a greater extent. In both groups the degree of h.d.ch. was not correlated with the localization or the extent of the leukemic

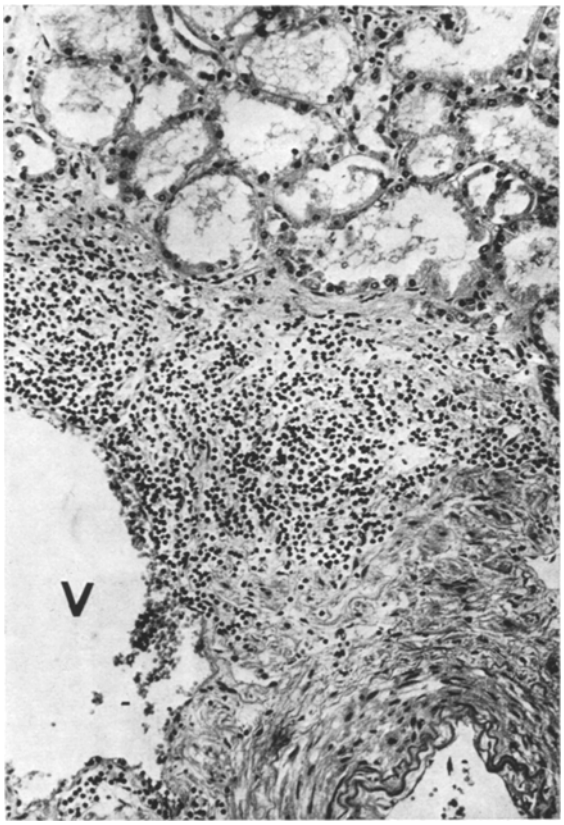

Fig. 2. Paravascular focal leukemic infiltrate in the corticomedullary border region of the kidney. *V* vein. CLL. Male, 63 years old. H & E. ×140

proliferation. In MML h.d.ch. was also not correlated with the number of monocytes of the renal infiltrates or the leukemic proliferation as a whole. All cases of MML with more pronounced h.d.ch. were complicated by secondary or unrelated accompanying diseases which can also cause h.d.ch., e.g. hemorrhagic diathesis necessitating repeated blood transfusions, postoperative ileus, suppurative bronchopneumonia, postacute proliferative glomerulonephritis and pyelonephritis.

Metastatic Calcinosis, Nephrocalcinosis. In one case of the 18 cases of MML a hypercalcemia syndrome had developed, which resulted in metastatic nephrocalcinosis.

Secondary Uric Acid Diathesis. Intratubular precipitates could be demonstrated in 3 cases with macroscopically detectable and clinically known hyperuricuria and in 2 other cases of MML.

Infectious Interstitial Alterations. Acute suppurative pyelonephritis, sometimes with abscesses, was found in 3 out of the 18 cases of MML, whereas it was absent in all cases of CLL. Fibrosis of the cortex and medulla not related to the leukemic infiltrates was more frequent in CLL and in most of the cases associated with arteriosclerotic vascular changes.

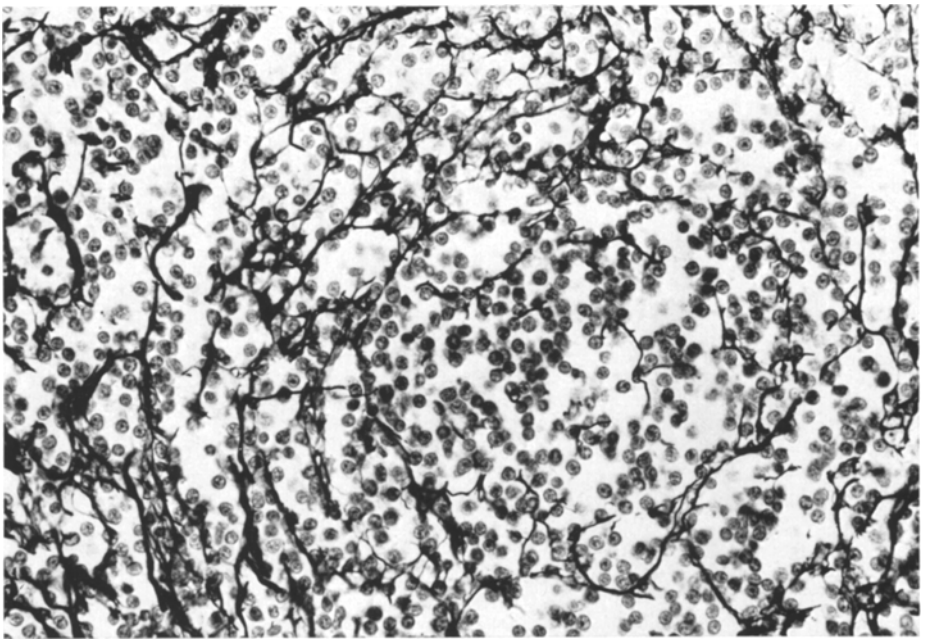

Fig. 3. Pseudofollicular arrangment of cells and fibers within a leukemic infiltrate. Partly thick fibers, fiber spurs. CLL with tumor formation. Male, 62 years old. Gomori. ×350

Interstitial Edema. In the absence of infectious interstitial alterations, interstitial edema was found in only one case from each leukemia group: in one man who suffered from MML with hypercalcemia syndrome and postoperative renal failure, and in one women with CLL and obstruction of the lower urinary tract due to prolapse of the uterus.

Morphological Features of Acute Renal Failure

According to Schubert (1968), the morphological criteria for acute renal failure are diffuse widening of the renal tubules, pigmented cylinders, osmotic nephrosis, crystalline precipitates and/or mixed lymphoplasmacytic infiltrates in the corticomedullary border region. In 4 out of the 18 cases of MML and 2 out of the 9 cases of CLL acute renal failure could be diagnosed since at least 3 of the mentioned criteria were found. Seven further cases of MML and 4 cases of CLL showed two of the above criteria. In these cases acute renal failure could be assumed from the other autopsy findings and clinical symptoms. The features of acute renal failure and the degree of leukemic infiltration were not correlated. All of our cases with these features were complicated by an accompanying or secondary disease which can cause acute renal failure per se.

Discussion

According to several reports, the kidneys of patients suffering from leukemia disclose leukemic infiltration in 50–100% of the cases (Wentzel and Bergheiser,

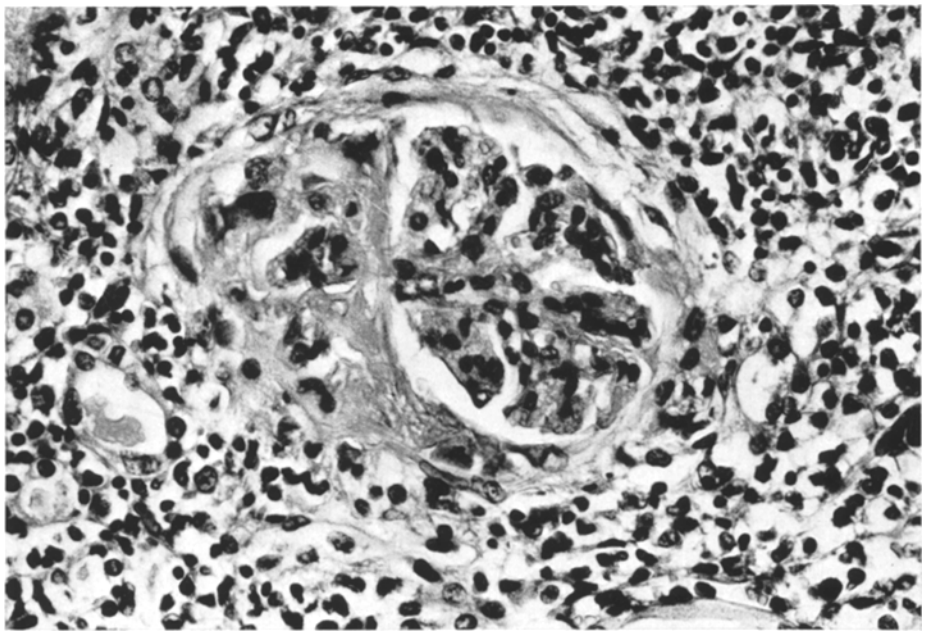

Fig. 4. Glomerulus within a leukemic infiltrate. Glomerular lesions of the compressive type. MML. Male, 68 years old. H & E. ×350

1955). We found renal leukemic infiltration in 17 out of 18 histologically examined cases of MML and in 8 out of 9 cases of CLL. Most of the infiltrated kidneys showed no excessive increase in weight, which agrees with the findings of Richmond *et al.* (1962). On the other hand, all greatly enlarged kidneys in cases of leukemia are probably infiltrated to various degrees. The renal enlargement, however, is neither constant nor does it depend on the degree of leukemic infiltration (Sternby, 1955; Lusted *et al.*, 1958; Frei *et al.*, 1963).

In all of our cases uremia was not directly correlated to the distribution or degree of leukemic infiltration of the kidney. The renal failure in the cases of MML showed no correlation to the percentage of monocytes in the leukemic infiltrates in the kidney, bone marrow, spleen or liver. To what extent hyperlysozymemia causes disturbances in renal function (azotemia in half of the cases studied by Pruzanski and Platts (1970)!) will have to be determined in clinical investigations. We could not find a characteristic morphological marker for the apparently combined glomerulo-tubular renal dysfunction in MML, as described by the authors mentioned above. Osserman and Azar (1969) reported h.d.ch. of the tubular epithelium and alterations of mitochondria and nuclei in cases of MML with hyperlysozymemia.

In cases of MML we observed a much higher degree of h.d.ch. than in cases of CLL. All but one of our cases of MML showed a well differentiated monocytic proliferation. Therefore, most of them should have been associated with an increase in the blood lysozyme value. In some cases of MML, h.d.ch. was not restrict-

ed to the proximal tubules (see Klockars *et al.*, 1974). However, in 5 cases of MML with a large number of monocytes and great leukemic infiltration of the bone marrow and spleen—in some cases there was excessive splenomegaly—no such tubular lesions could be found and there was no necrosis of the tubular epithelium. We think that the h.d.ch. found in our cases of MML was, like that of CLL, related to the accompanying or secondary diseases which can cause primary proteinuria and tubular protein reabsorption. Experimentally, in rats with exogenous or endogenous hyperlysozymemia, lysozyme was found in the epithelial cells of the tubules in variably large cytoplasmic droplets and alterations of the nuclei and mitochondria were detected (Osserman and Azar, 1969; Klockars *et al.*, 1974). However, the lysozyme alone could not have caused these alterations (Klockars *et al.*, 1974). It should be stressed that h.d.ch. is neither a sign of nor a parameter for tubular damage, nor is it a regressive lesion (Randerath and Bole, 1959; Zollinger, 1966). Our observations agree with those of Zollinger (1966) and indirectly with those of Klockars (1974).

The absence of specific tubular lesions in cases of MML, however, does not exclude the possibility of functional damage. For instance, Mir and Delamore (1974) discussed the competitive inhibition of tubular function through reabsorption of unidentified metabolites released from the leukemic cells in cases of acute myeloid leukemia.

The author is grateful to Mr. K.-H. Tedsen for his excellent technical assistance and to Mrs. M. Soehring for translation and secretarial help.

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