Virchows Arch. path. Anat. 343, 189—196 (1968)

The Vasculature of the Adrenal Gland in Neoplasia and Hyperplasia*

An Angiographic and Micro-Angiographic Study

TORE EKSTRÖM**, BIÖRN IVEMARK and CURT LAGERGREN
Departments of Surgery, Pediatric Pathology, and Diagnostic Radiology, Karolinska sjukhuset, Stockholm, Sweden

Received September 10, 1967

Das Gefäßmuster der Nebenniere in Neoplasie und Hyperplasie

Eine angiographische und mikroangiographische Untersuchung

Zusammenfassung. Eine Serie von 28 Nebennieren mit Rinden- oder Marktumoren, Hyperplasie und Metastasen wurde mikroangiographisch und histologisch untersucht. In einigen Fällen war ein Vergleich mit klinischen Angiogrammen möglich. Das Gefäßmuster zeigte alle Übergänge vom normalen Verhalten, über Hyperplasie, Adenom, Phäochromocytom, Neuroblastom bis zum Krebs. Es ist unmöglich, in einer Grenzzone zwischen den einzelnen Formen allein auf Basis des Gefäßmusters zu unterscheiden.

Summary. Micro-angiographic and histologic examinations were performed on a series of 28 adrenal glands with cortical or medullary tumors, and with hyperplasia and metastases; in some instances the results were compared with clinical angiograms. The vascular patterns varied by transitions from the normal adrenal gland *via* hyperplasia, adenoma, pheochromocytoma, neuroblastoma to cancer. In the border zones it was impossible to differentiate between the forms solely from the vascular pattern.

Further clinical details are available in the Department of Pediatric Pathology.

The accurate diagnosis and location of pathologic alterations in the adrenal glands has long presented a problem, as is evident from the numerous articles on the subject that have been published in the last few years. As micro-angiographic examination of specimens has disclosed vascular changes that would probably be visualized by angiographic examination *in vivo* (LAGERGREN, 1967; LAGERGREN and LINDBOM, 1962) this technique was applied in the examination of the vascular pattern in the more common neoplastic changes of the adrenals. To provide a background to such a study an examination was first made of the micro-angiographic conditions in the normal adrenal gland (IVEMARK et al., 1967). The X-ray diagnostic aspects have been dealt with in a separate paper (LAGERGREN, 1967).

Material and Method

The material consists of 28 adrenal glands, 26 of which had been removed because of pathologic alterations diagnosed on the basis of clinical and radiologic findings. Two of the glands were autopsy specimens from a case of adrenal neuroblastoma. The material may be grouped as follows: *A.* Four hyperplastic adrenal glands from 3 patients, and 10 glands with cortical tumors, 8 of them adenomas and 2 carcinomas. *B.* Seven medullary tumors, 6 of them pheochromocytomas and 1 primary neuroblastoma. *C.* Seven adrenals with metastases, the primary foci in 6 cases being the mammary glands and in one a neuroblastoma of the other adrenal. Except for the case of neuroblastoma, a boy of 16 months, all the specimens were from

* This investigation has been supported by grants from Adolf and Agnes Wallgrens' Fund.

** Present address: Department of Surgery, Centrallasarettet, Eskilstuna, Sweden.

adults. They were injected with a 7.5 per cent aqueous suspension of barium sulphate (Micropaque®) and prepared for micro-angiographic examination by techniques that have been described elsewhere (LAGERGREN and LJUNGQVIST, 1965; IVEMARK et al., 1967). Five of the adrenal adenomas were injected with opacifying medium through an adrenal vein, while 23 were injected from the arterial side.

Results

Alterations in the Adrenals

Hyperplasia

Radiographic Findings. In 2 of the 3 cases pre-operative aortography with filling of the adrenal arteries had been performed. In one of them an adrenal was enlarged and displayed marked hypervascularization, and in the other there were no abnormalities.

Morphologic Findings. The basic pattern of the gland was normal but the sinusoids were denser and appeared to have increased in number. In their width and mode of ramification they were normal, as was the arterial pattern, except for an occasional slight widening of the arterial branches. There was no definite micro-angiographic difference between the histologically distinct types of hyperplasia. Where no distinction between hyperplastic tissue and adenoma could be made histologically, the micro-angiography visualized the basic vascular pattern of the adrenal. This technique thus helped to rule out the possibility of adenoma.

Tumors of the Adrenal

Adenoma

Radiographic Findings. Of the 8 cases of adenoma 7 had undergone aortography prior to operation. In 6 of these, adrenal enlargement with hypervascularization were observed, and 2 also exhibited pathologic alteration of vessels. In one case conditions were normal.

Morphologic Findings. The histologic check of the adenomas showed satisfactory filling with contrast medium, and likewise for the adjacent adrenal glands.

A notable feature of the adenoma vasculature was a general enlargement of the vessels of the normal and hyperplastic glands. In some cases there were sinusoidal sprays, but these were irregular as regards both course and density of the vessels (Fig. 1). The arteries displayed a less systematic pattern than in normal glands. In some of the adenomas there were vestiges of the sinusoidal pattern (Fig. 1 A), while others presented a more extreme pathologic picture, with irregular width and a serpentine course of the vessels (Fig. 2). The vascular density varied from one adenoma to another and within a particular gland. There was no evident correspondence between the vascular pattern and the histologic structure.

Carcinoma

Radiographic Findings. The 2 cases in this group had had a pre-operative aortographic examination, which had disclosed large, moderately vascularized tumors with vessels having an abnormal course.

Morphologic Findings. The degree of filling was satisfactory. There were no structures reminiscent of the characteristic normal vascular pattern, there being only pathologic vessels with abnormal course and wall structure; they varied in

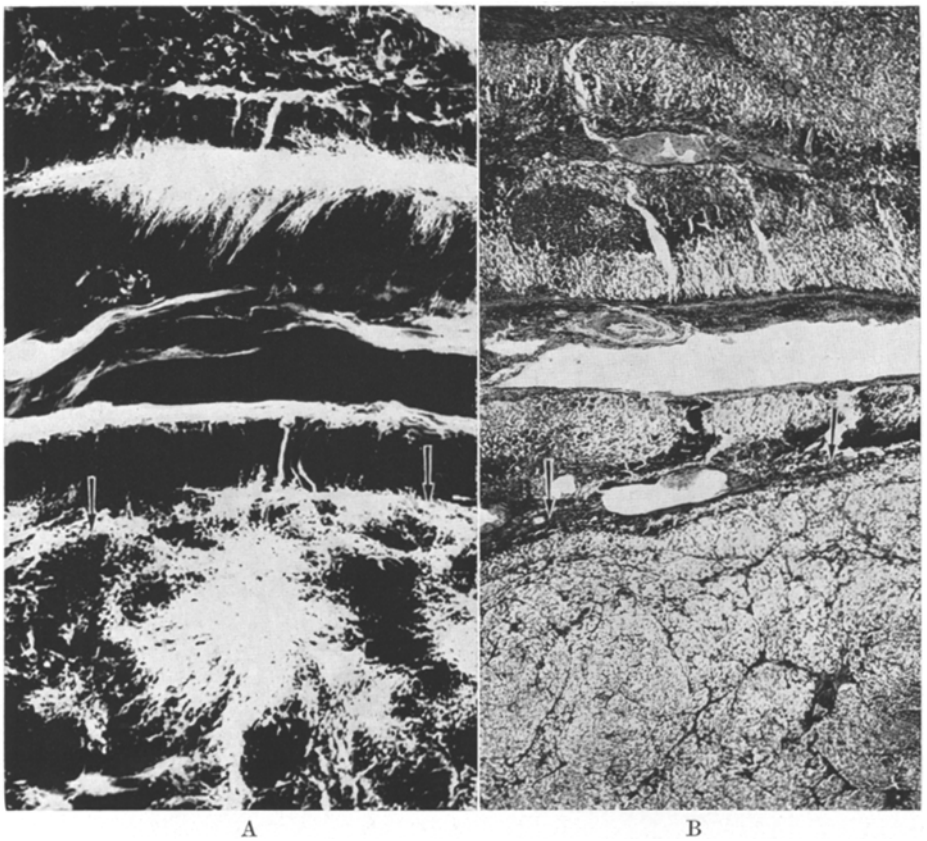


Fig. 1 A and B. Adenoma of the adrenal cortex with hyperaldosteronism. A Micro-angiogram. Normal adrenal structure with parallel sinusoidal sprays in the upper part of the film. *Center*, a capsule vessel and, *below*, the adenoma (*arrows*) with visualization of the widened sinusoidal vessels. × 14,4 (reduced $^{9}/_{10}$). B Histologic section from the corresponding area with lipid-rich glomerulosa tissue. × 16

density in different parts of the tumor (Fig. 3). Both cases presented histologically similar pictures of pleiomorphic solid carcinoma, with evidence of a high mitotic frequency. There were extensive areas of necrosis and hemorrhage and a few small areas of calcification.

Pheochromocytoma

Radiographic Findings. All 6 cases composing this group presented similar clinical features with hypertensive crises and elevated catecholamine levels. Four of them had undergone aortography prior to operation. In only one were pathologic vessels seen, and then they were few and small; 2 showed moderate hypervascularity. In all 4 there was enlargement of the affected adrenal gland, with stretching of the vessels. In 2 cases aortography had at first shown normal conditions but subsequently pathologic changes. In the 2 cases in which no vascular examination had been performed evidence of adrenal enlargement had been observed in plain films.

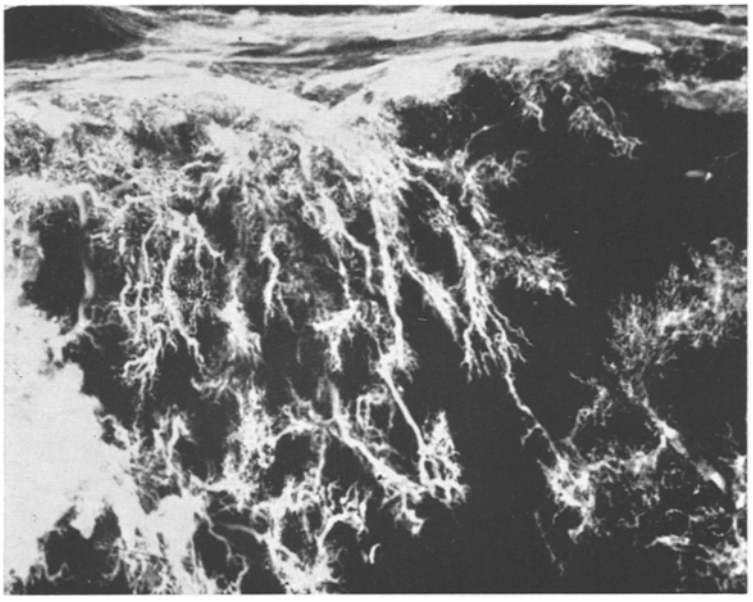


Fig. 2. Adenoma of the adrenal cortex with hyperaldosteronism. Micro-angiogram with irregular pathologic vessels, serpentine in segments and no evidence of the normal vascular pattern of the adrenal. × 16

Morphologic Findings. In 5 cases there was satisfactory filling throughout the gland and in the sixth in part of it, but there were also extremely wide partially filled vessels within which the medium formed islands.

Three distinct vascular patterns were recognized:

I. In one case with a vascular picture quite distinct from the rest there were extremely wide vessels in which the medium formed islands (Fig. 4). Between these there were tufts of comparatively wide, irregular, tortuous vessels, some segments of which were straight and others serpentine. There were extremely few vessels of capillary width.

The microscopic structure was fairly uniform, with pleiomorphic cells in solid cords and incipient invasion of vessels and capsule. The histologic examination, too, showed numerous thin-walled pathologic vessels.

II. Three cases of an intermediate type, with dense sprays of serpentine, irregular vessels situated in groups, varying in density in different parts of the tumor. The vessels were fairly homogenous in caliber and much narrower than those of type I. Histologic examination disclosed a less pleiomorphic structure than in group I, with solid cords and round, partly chromaffine, cells.

III. This group comprised 2 cases in which the vascularity was less marked with fewer vessels than in the previous 3 forms. There were considerable differences in caliber, with fairly few wide vessels and numerous extremely narrow vessels, forming a spider web pattern (Fig. 5). This picture was confirmed by the histologic examination. The tumors consisted of wide solid cords of large, light and partly chromaffine cells displaying moderate polymorphism.

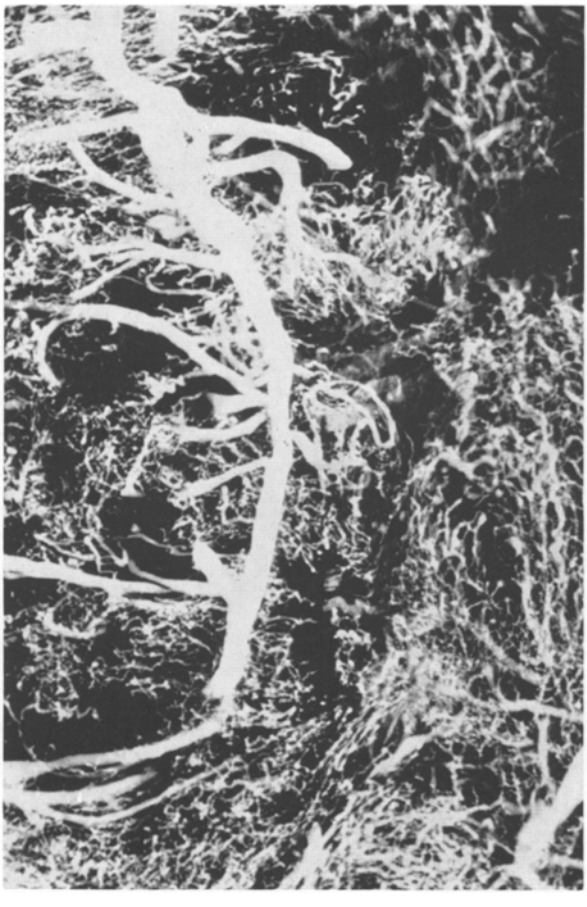


Fig. 3. Carcinoma of the adrenal cortex. Micro-angiogram with pathologic vessels, serpentine in their course and irregular in caliber. × 16

Neuroblastoma

Radiographic Findings. Angiography performed several months prior to death had disclosed displacement of vessels but no pathologic ones or hypervascularity.

Morphologic Findings. Opacifying medium was injected post mortem *via* the aorta into the abdominal organs, which had been removed *en bloc.* Satisfactory filling was obtained in both adrenals (Fig. 6). The right one measured 6 × 5 × 5 cm and was almost entirely replaced by tumor; the left gland was of normal size.

Microangiograms of the primary tumor revealed closely packed, serpentine and narrow pathologic vessels. The vascular pattern recalled that of pheochromocytoma, particulary type III (Fig. 5).

Metastases

In the 6 adrenals with metastases the micro-angiograms showed pathologic serpentine vessels in the periphery of the metastases, while the centers of the foci

Fig. 4

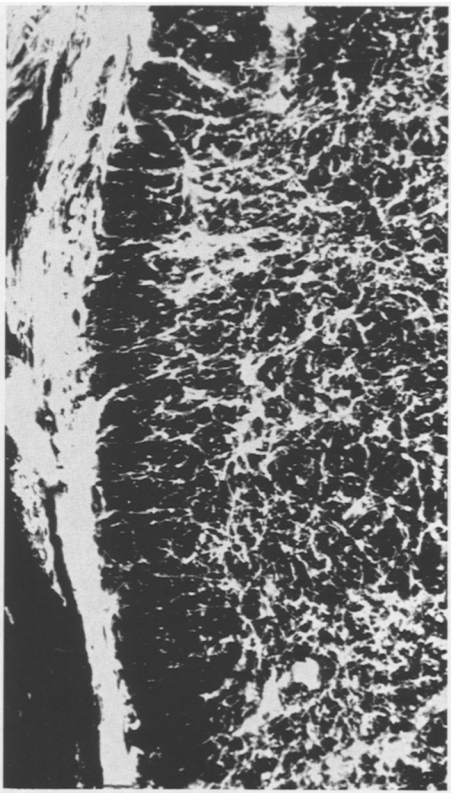


Fig. 5

Fig. 4. Pheochromocytoma. Micro-angiogram of a nest extremely wide pathologic vessels. *Cf.* the other micro-angiograms with the same magnification. × 14,4 (reduced $^{9}/_{10}$)

Fig. 5. Pheochromocytoma. Micro-angiogram with formations of narrow vessels and occasional coarse trunks. × 14,4 (reduced $^{9}/_{10}$)

were "empty". These vessels showed a distinct deviation from the normal pattern for the adrenal gland.

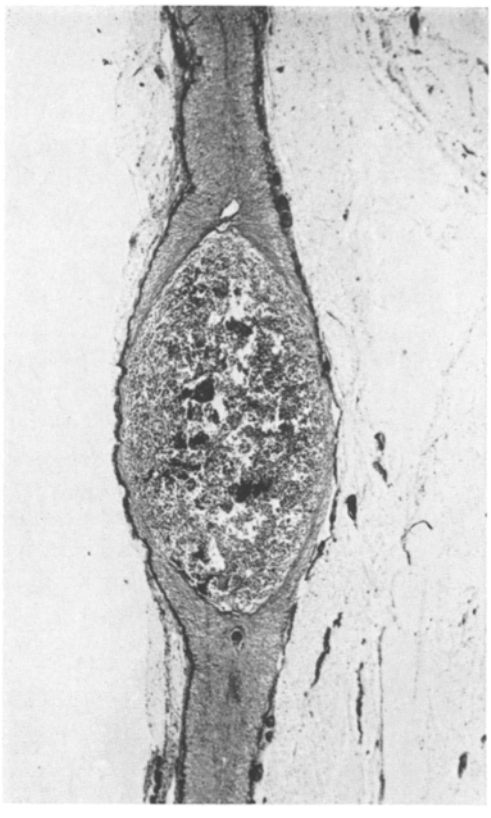
The metastatic neuroblastoma, however, contained numerous vessels, while the rest of the surrounding adrenal was poorly filled (Fig. 6).

Discussion

The study showed that all the forms of adrenal tumor differed in their vascular pattern from that of the normal gland (IVEMARK et al., 1967). This difference was less marked for the adenomas, in which there was often a coarsening of the normal cortical structure, with a number of sinusoidal sprays. In other types of adenomas, on the other hand, there were pathologic vessels large enough to be visualized radiologically. Even within the adenoma group there were thus variations, ranging from the practically normal pattern to one typical of a tumor.

The clinical differential diagnosis between adenoma and hyperplasia can be facilitated by angiography when the tumor has pathologic vessels that can be

A



B

Fig. 6A and B. Neuroblastoma metastasis in the adrenal gland. A Micro-angiogram of the adrenal metastasis from a neuroblastoma. The hypervascularization of the tumor focus is distinctly seen. × 14,4 (reduced $^{9}/_{10}$). B Histologic section of the same part as in Fig. 6A. Hematoxylin and eosin. × 14,4 (reduced $^{9}/_{10}$)

visualized radiographically. In the absence of such vessels it is impossible to perform a radiographic differential diagnosis between hyperplasia and adenoma unless the adenoma is extremely large. In hyperplasia of the cortex micro-angiographs show that while the pattern of the normal adrenal is retained there appears to be an increased vascularity.

The observed coarsening of the supplying arterial branches indicates an adaptation of the vascular architecture to the increased functional activity of the gland. This true hypervascularity in some cases increases the chance of diagnosing hyperplasia by angiography.

In the cases of carcinoma of the adrenal gland in this small series micro-angiography disclosed numerous pathologic vessels, and the normal pattern was abolished. Here the problem is to distinguish adrenal carcinoma from carcinoma of the surrounding organs or pheochromocytoma.

The variation in the vascular pattern of pheochromocytoma is striking. This tumor is usually described as highly vascularized (Goodwin, 1961) but it is evident from the present series that this is not always so, there being pheochromocytomas

that have relatively few vessels. It is then necessary to rely on the clinical picture — including hypertensive crises and elevated catecholamine levels — for a differential diagnosis (PALMIERI et al., 1961), the angiographic examination providing only an indication of which adrenal is affected, and not what the nature of that affection is. A small, poorly vascularized pheochromocytoma cannot be distinguished from an adenoma on the angiogram. Histologic grading of malignancy of a pheochromocytoma is difficult and the authors' vascular studies provide no help in this direction.

The sole case of neuroblastoma also provides no assistance in the angiographic differential diagnosis with respect to, for instance, Wilms' tumor. It is of some theoretical interest, however, that the vascular pattern of neuroblastoma is reminiscent of that of pheochromocytoma, both being medullary tumors.

It is thus evident that there is a gradual transition of the vascular pattern from the normal to the hyperplastic adrenal gland, with no obvious increase in vascularity that can be seen in the angiogram; there is also progress from a hypervascularized hyperplasia to a hypervascularized adenoma, from an adenoma with pathologic vessels to a poorly supplied pheochromocytoma, and from a highly vascularized pheochromocytoma to carcinoma. Within the transitions between these distinct angiographic forms it is impossible to perform a differential diagnosis on the basis of the films.

References

GOODWIN, W. E.: Chapter 47 "Adrenal angiography" in "Angiography" (edit. H. L. ABRAMS). Boston: Little, Brown & Co. 1961.

IVEMARK, B., T. EKSTRÖM, and C. LAGERGREN: The vasculature of the developing and mature human adrenal gland. Acta paediat. Scand (Uppsala) **56**, 601 (1967).

LAGERGREN, C.: Angiographic changes in the adrenal gland. Amer. J. Roentgenol. (in press).

—, and Å. LINDBOM: Angiography of peripheral tumors. Radiology **79**, 371 (1962).

—, and A. LJUNGQVIST: The arterial vasculature of renal pelvic carcinomas. An angiographic, microangiographic and histologic study. Acta chir. scand. **130**, 321 (1965).

PALMIERI, G., D. IKKOS, and R. LUFT: Malignant pheochromocytoma. Acta endocr. (Kbh.) **36**, 549 (1961).

Dr. BIÖRN I. IVEMARK
Inst. för pediatrisk patologi Karolinska sjukhuset
Stockholm, 60/Sweden