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AJNR

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S Halpin and D Kingsley

AJNR Am J Neuroradiol 1993, 14 (1) 119-122

<http://www.ajnr.org/content/14/1/119>

This information is current as
of September 23, 2024.

Disappearance of Cerebral Calcification as a Sign of Tumor Growth

Shawn Halpin and Derek Kingsley

Summary: Calcification occurs in many benign and malignant neurologic disorders. We describe two patients with cerebral glioma, in whom the disappearance of cerebral calcification was evidence of local malignant change. We discuss the underlying chemical mechanisms that result in tissue calcification, and postulate that calcification may disappear in the presence of a malignant tumor because of a decrease in the pH of the microenvironment.

Index terms: Brain neoplasms, calcification; Glioma

Cerebral calcification may occur in benign and malignant tumors (1–5), metabolic disorders (6), vasculitic/ischemic insults (7, 8), parasitic or viral infection (9, 10), and following radiotherapy (11). It is rare for it to disappear on follow-up computed tomography (CT). Although this phenomenon is well recognized in scar carcinoma of the bronchus (12), and in pineal germinoma (13), where malignant tumor engulfs preexisting calcification, it has not, to our knowledge, been reported in other intracranial sites. We describe two patients in whom intracerebral calcification was engulfed by local high-grade glioma, and propose a biochemical mechanism for this phenomenon. Disappearance of calcification within the brain is an ominous sign, and appears to indicate a high-grade tumor.

Case 1

A 43-year-old white woman was admitted with a 7-week history of headache, intermittent vomiting, and more recent slurring of speech. On examination, there was mild bilateral pyramidal weakness, and sensory inattention to the left.

CT revealed a large, right-sided temporoparietal lesion, with displacement of midline structures and patchy, peripheral contrast enhancement (Figs. 1A and 1B). Subsequent surgical biopsy confirmed the preoperative diagnosis of a high-grade astrocytoma. After partial excision, radiotherapy was undertaken in a dose of 60 Gy over 4 weeks, with clinical and radiologic evidence of regression of tumor.

This treatment was supplemented with multiple agent chemotherapy. Follow-up CT scans 8 months after surgery showed extensive calcification within the tumor bed, and little residual tumor (Fig. 1C).

Six months later, there was clinical deterioration, and CT showed a large local recurrence, with erosion and disappearance of the calcification, and extension of tumor into the corpus callosum and contralateral hemisphere (Figs. 1D and 1E). The patient died shortly afterwards.

Case 2

A 33-year-old white man was admitted with a history of increasing frequency of seizures, headache, and more recently, drowsiness. Three years previously, two small foci of calcification had been noted at CT in the inferior part of the right temporal lobe (Fig. 2A and 2B), but the patient had been lost to follow up.

On examination, there was a left hemiparesis and bilateral papilloedema. On CT, previously noted calcification was no longer present (Fig. 2C), having been replaced by a large enhancing tumor within the right temporal lobe with considerable mass effect and vasogenic edema (Fig. 2D).

The patient underwent partial removal of the tumor, which was determined histologically to be a high-grade glioma. He is at present completing a course of postoperative radiotherapy.

Discussion

Calcification occurs in a wide variety of conditions (14). According to the degree of malignancy, and histological type, it may be seen in 15%–60% of gliomas (2, 3, 15), or may follow radiotherapy and presumed cell death (11, 16), as in one of these cases. It is more prone to occur in certain areas of the brain, such as the basal ganglia, which are rich in endogenous iron and calcium (17, 18).

A cellular mechanism of calcification has been suggested. In the normal cell, there is a calcium gradient across the cell membrane, with the extracellular calcium concentration being 10^4 times

Received February 21, 1992; revision requested March 28; revision received April 27 and accepted May 4.

Both authors: Lysholm Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, London, WC1N 3BG, England. Address reprint requests to Dr Halpin.

AJNR 14:119–122, Jan/Feb 1993 0195-6108/93/1401-0119 © American Society of Neuroradiology

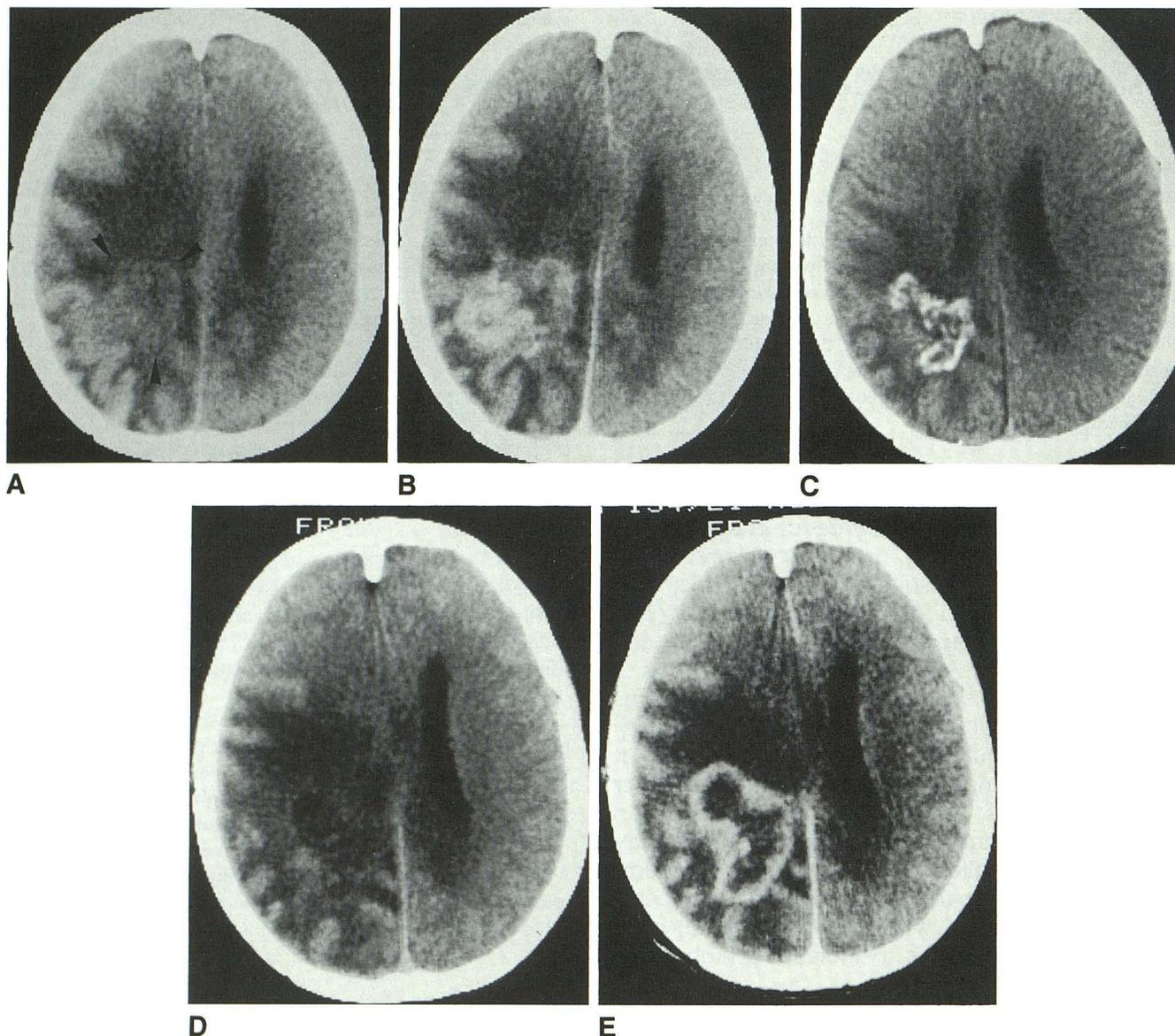


Fig. 1. Axial CT sections A, C, and D were taken following contrast enhancement; B and E are unenhanced. An enhancing right parietal tumor is present (A and B, arrowheads), which did not contain calcification. There is mass effect and considerable vasogenic edema. Following radiotherapy and chemotherapy, serpiginous calcification is seen (C), with partial resolution of the mass effect and clinical improvement. Six months later, the calcification has been replaced by aggressive tumor regrowth (D and E).

that inside the cells. This gradient is maintained by ATP-dependent pumps in the mitochondria, endoplasmic reticulum, and cell membrane. In the presence of prolonged hypoxia, this pump fails. There is an influx of calcium into the cell, resulting in calcium phosphate deposition which, in a stable microenvironment, may eventually be converted into calcium hydroxyapatite. There follows crystal proliferation, and extension of calcification into the extracellular space (19, 20). Calcification, therefore, follows cell death (20). It is promoted by the presence of alkaline phosphatase (17, 21), which is most effective in an alkaline

milieu (17), and is abundant in degenerative tissues (1). Necrotic or degenerative tissues are likely to be alkaline due to their low metabolic rate and, hence, reduced carbon dioxide production (1). Magnetic resonance (MR) spectroscopy has confirmed that gliomas, especially those of high grade, are alkaline (22, 23). A pH rise has also been noted in human glioma following chemotherapy (24), and this may partly explain the appearance of calcification in our first patient. Therefore, it is not difficult to understand how necrotic tissue within an alkaline tumor can become calcified.

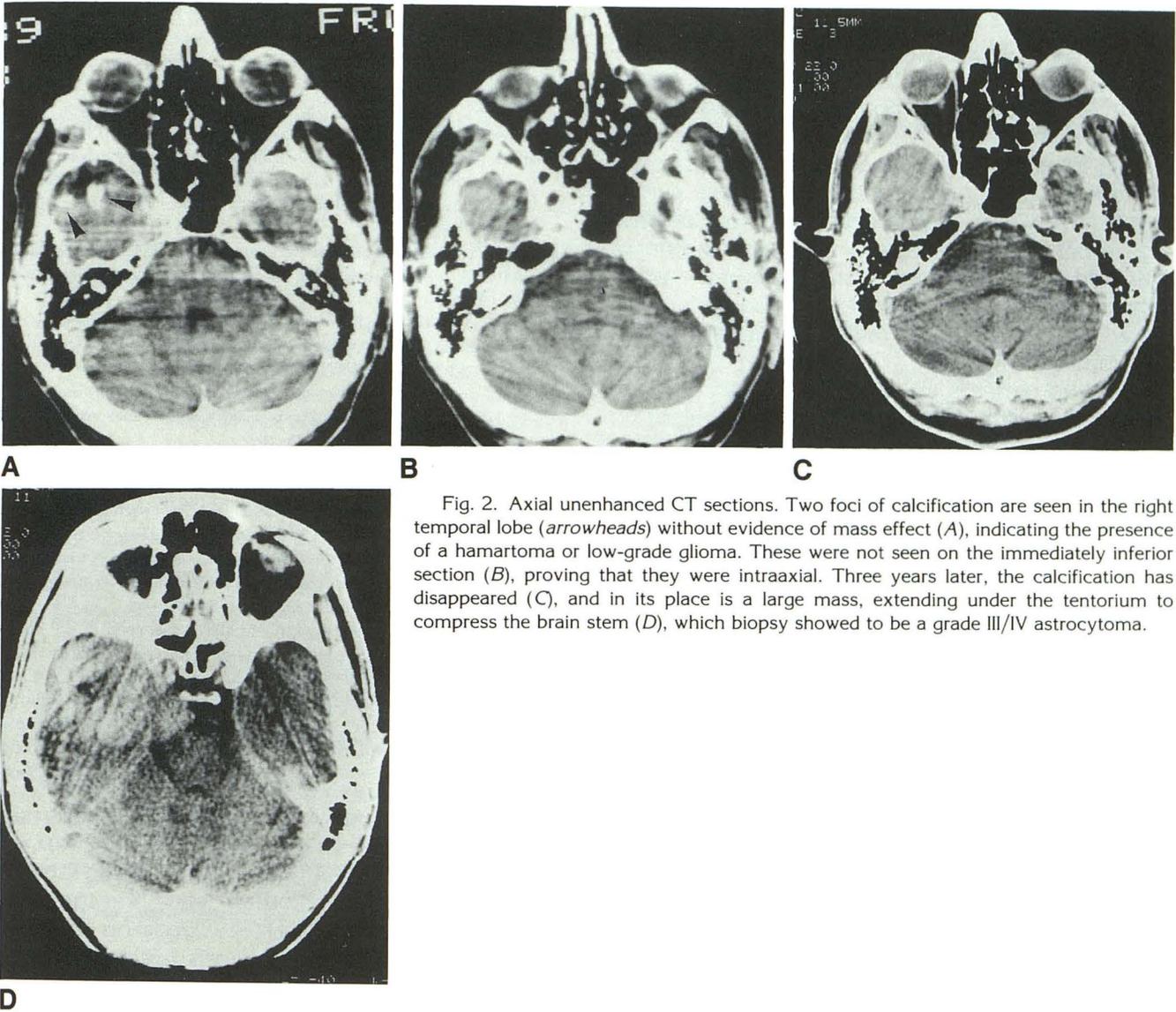


Fig. 2. Axial unenhanced CT sections. Two foci of calcification are seen in the right temporal lobe (*arrowheads*) without evidence of mass effect (A), indicating the presence of a hamartoma or low-grade glioma. These were not seen on the immediately inferior section (B), proving that they were intraaxial. Three years later, the calcification has disappeared (C), and in its place is a large mass, extending under the tentorium to compress the brain stem (D), which biopsy showed to be a grade III/IV astrocytoma.

It is more difficult to understand exactly what happens when calcification is apparently engulfed by tumor, as in our patients. We propose that this phenomenon may be explained by a change in local tissue pH. Rapidly growing tumors may outgrow their blood supply, and become relatively ischemic, resulting in the production of lactate and a fall in the pH of the microenvironment. In an attempt to negate the rising intracellular H^+ ion concentration, there is a reversal of the normal Na^+/H^+ gradient (25–27). Thus, the extracellular pH will tend to fall further. As long as some tumor cells remain ischemic but viable, they will tend to exist in an acid rather than an alkaline medium. Calcium phosphate is relatively soluble in acid solutions (29), and since intratumoral calcium deposits are relatively unstable, prolonged ischemia within the tumor could result

in the dissolution of calcium deposits. Indeed, the stability of the microenvironment may be important: once calcium is deposited, it exists in equilibrium with its surroundings; the type of calcium deposit formed depends on local pH, enzyme activity, etc, and will not always be stable. A rapidly fluxing chemical milieu will not permit crystal formation; defective apatites are formed, for example, in acidic media (28). Although spectroscopy shows high-grade gliomas to be alkaline overall (22, 23), these measurements were made in relatively large volumes of the tumor (a minimum of 1 cm^3); it is quite conceivable that parts of it vary in pH—indeed it would be surprising if this were not the case.

The disappearance of calcification in our patients coincided with other radiologic evidence of local tumor progression, and it is safe to presume

that the loss of calcification was caused by the tumor itself. There was no biochemical abnormality to account for this; the patients' serum electrolytes remained normal throughout their illness.

The situation is analogous to the destruction of normal pineal calcification by a pineal germinoma (13), which is well described. Similar findings are frequently seen in adenocarcinoma of the lung—the so-called scar carcinoma—when disappearance of a calcified lung nodule is associated with a soft-tissue mass as evidence of the developing tumor (12).

The two patients we describe did not undergo MR imaging, but it is interesting to speculate on the relative merits of CT and MR. Although the enormously increased sensitivity of MR to changes in tissue characteristics would undoubtedly have demonstrated these aggressive tumors, MR is, of course, insensitive to the presence of calcification (30) and may not have detected calcification in our patients, thus missing a valuable indicator of malignancy.

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