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Expression of basic fibroblast growth factor, nerve growth factor, platelet-derived growth factor and transforming growth factor-β in human brain abscess

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Abstract We correlated the histopathological findings of six human brain abscesses with the expression of basic fibroblast growth factor (bFGF), nerve growth factor (NGF), platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGFβ). The clinical courses ranged from 1 month to 1 year and viridans streptoccus was the major pathogen. In early abscesses, we demonstrated strong bFGF and moderate NGF and PDGF immunoreactivities in neutrophils and monocytes/macrophages infiltrating the abscess wall and in the fibrin layer lining the abscess center. In the subacute cases, growth of capillaries and fibroblasts into the fibrin layer and deposition of collagen resulted in the formation of a mesodermal layer between the abscess center and the outer gliotic layer. The proliferative non-neural cells (endothelial cells, fibroblasts and glial cells) expressed mild to strong bFGF, NGF and PDGF immunoreactivities, while strong TGFβ staining was seen in the extracellular matrix. A loss of growth factor expression and increased fibrosis was seen in the chronic case. These findings suggest that bFGF, NGF, PDGF and TGFβ produced by the continued influx of leukocytes and by the proliferating non-neural cells may mediate various steps of defense mechanisms and wound healing such as angiogenesis, fibrogenesis and gliosis.

Key words Brain abscess · Fibroblast growth factor Nerve growth factor · Platelet-derived growth factor Transforming growth factor-beta

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Introduction

The histological findings of brain abscess in human and experimental animals have been well documented [8, 17, 48, 50]. In the experimental model, there is a period of acute suppurative cerebritis from 1–3 days with leukocytic exudation and edema surrounding an area of necrosis. The abscess wall is at first poorly defined and is composed of granulation tissue infiltrated by neutrophils, macrophages and lymphocytes. Proliferation of capillaries, fibroblasts and deposition of reticulum fibers and collagen in the granulation tissue creates a mesodermal zone between the necrotic center and the outermost gliotic zone. After 14 days, the abscess is encapsulated and appears on computerized tomography as a ring enhancing lesion surrounding a large central radioluscent area. The leakage of contrast medium is presumably due to the presence in the abscess wall of newly formed blood vessels which lack a blood-brain barrier.

Angiogenesis is a normal response to many forms of injury and is seen in brain abscess, hematoma and ischemic brain infarct [18, 31, 32]. Gliosis is likewise a universal response of brain to injury [10, 35, 43]. Fibrosis and collagen deposition, on the other hand, are less frequently encountered in brain except in abscess and in certain neoplasms. The biochemical and molecular mechanisms responsible for the different tissue response are not clear. It is generally known that cell proliferation and differentiation during development and wound healing are mediated by cell to cell interaction through polypeptide growth factors [15]. Basic fibroblast growth factor (bFGF), platlet-derived growth factor (PDGF) and transforming growth factor-β (TGFβ) are growth factors implicated in cell proliferation, fibrogenesis and wound healing [22, 36, 45]. In experimental brain infarct, enhanced expression of bFGF in neurons adjacent to the infarct was followed by glial and vascular proliferation [34]. In studies on peripheral nerve and muscle injuries, expression of

bFGF, nerve growth factor (NGF) and PDGF by infiltrating leukocytes was observed (unpublished data). These findings have prompted us to examine the correlation between the histologenesis of the brain abscess and the expression of bFGF, PDGF, TGFβ and NGF by participating cells.

Material and methods

The material consisted of six cases of brain abscess removed during surgery. The clinical symptoms ranged from 1 week to 1 year. On computerized tomography, all showed a ring enhancing thin capsule surrounding a large central hypodense area.

Production and specificity of the antibodies

The bFGF and PDGF antibodies were purchased from Oncogene Science (Uniondale, N.Y.). The bFGF antibody is a rabbit affinity-purified polyclonal antibody against peptide (AILFLPM) which corresponds to amino acid 147–153 of human bFGF. The specificity of the bFGF antibody was confirmed by the fact that positive immunoreactivity was abolished by prior incubation of the antibody (1 μg/ml) with 1 μg recombinant bFGF (Oncogene Science). The antibody does not show cross reactivity with acidic FGF on Western blotting. The PDGF antibody is an affinity purified rabbit polyclonal antibody raised against a peptide (TEVFEISRRLIDRTMA) corresponding to amino acids 109 to 124 of human PDGF BB. The pan-specific polyclonal TGFβ antibody purchased from R&D systems Inc. (Minneapolis) was raised against a mixture of purified recombinant TGFβ1, porcine TGFβ1,2 and amphibian TGFβ5. The NGF antibody purchased from Serotec (Oxford, England) is a polyclonal antibody raised against ultra pure 2.5S NGF, and its immunoreactivity was abolished by prior incubation of the antibody (1 μg/ml) with 1 μg ultra pure 2.5S NGF (Serotec). Polyclonal GFAP antibody was from Dako Co.

Immunohistochemistry

The formalin-fixed and paraffin-embedded specimens were cut at 4 μm and routinely stained with H&E, trichrome and Wilder's reticulum stains. Immunohistochemistry was performed according to the standard streptavidin-biotin peroxidase method using a Dako LSAB kit (Carpenteria, Calif.). After blocking in 3% H_2O_2 for 15 min to eliminate endogenous peroxidase and in a blocking solution (in the kit) for 20 min to eliminate non-specific binding, the sections were incubated in primary antibodies with the following dilutions: anti-bFGF 1:100 dilution, anti-PDGF 1:50, anti-TGFβ 1:100, anti-NGF 1:600, anti-GFAP 1:800 for 16 h at 4 °C. Subsequent to primary antibodies, the sections were sequentially incubated in biotinated secondary antibody for 1 h, streptavidin-peroxidase solution for 1 h at room temperature with rinsing with PBS three times between incubations. The sections were finally reacted in 3-amino-9-ethylcarbazole in the presence of 0.003% H_2O_2 for 15 min and counterstained with hematoxylin. Negative controls consisted of omitting primary antibody, and using irrelevant primary antibodies: polyclonal antibodies against epithelial membrane antigen and desmin.

Results

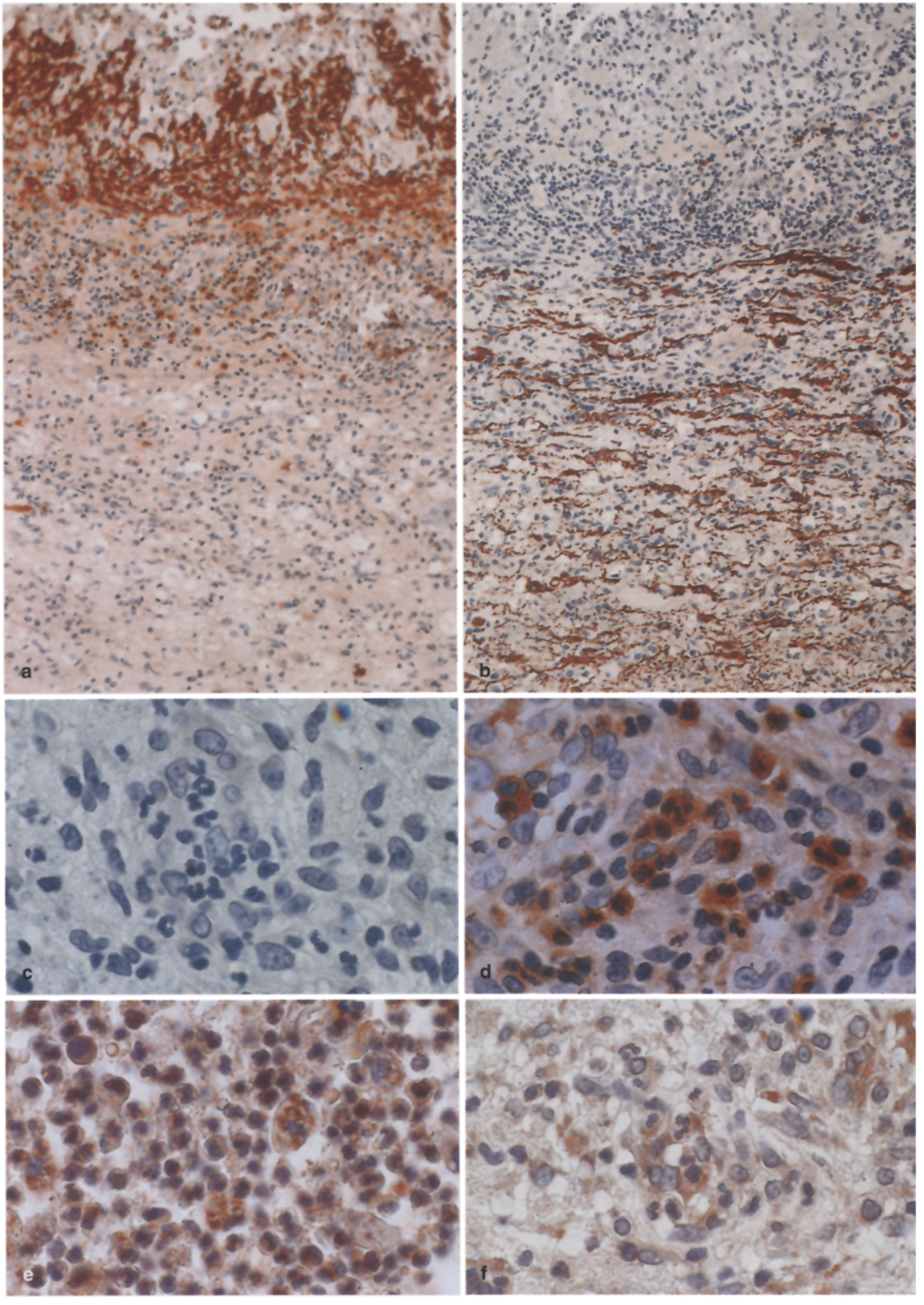
Early abscess

Case 1 and 2 had a clinical course of 1–3 weeks and represented an early stage of brain abscess. Culture obtained from the abscess yielded viridans streptococci in one case and streptococci sanguis in the other. Additionally, *Eikenella corrodens* and non-identified gram-negative bacilli were found in one case. The abscess center contained necrotic debris and leukocytes bordered by a fibrin layer (Fig. 1a). The abscess wall measured 1–2 mm and was composed of an inner layer of granulation tissue and an outer layer of horizontally oriented reactive astrocytes (Fig. 1a, b). The infiltrating monocytes and neutrophils in the granulation tissue exhibited strong bFGF, and weak to moderate NGF and PDGF immunoreactivities, while lymphocytes and plasma cells were unstained (Fig. 1c–f).

Evolving abscess

Cases 3–5 represented stages in the evolution of the abscess capsule. Bacterial culture yielded viridans streptococci as the major pathogen in all three cases. The abscess wall had increased to 2–3 mm in thickness with an inner zone of leukocytes and debris-laden macrophages containing immunoreactive NGF, bFGF and PDGF intracytoplasmic granules. The proliferating vascular endothelial cells and reactive astrocytes exhibited relatively strong staining for NGF and PDGF (Fig. 2a, b). A diffuse TGFβ immunoreactivity was noted in the extracellular matrix (ECM) in the form of a fibrillary network surrounding blood vessels and enmeshing the fibroblasts and leukocytes (Fig. 2c). A rich capillary plexus accompanied by reticulum and collagen grew perpendicularly into the fibrinous layer (Fig. 2d, e). With increased deposition and spreading of perivascular reticulum and collagen, a mesodermal layer between the abscess center and the outer gliotic layer was formed. There was a moderate diffuse NGF staining in the ECM of the abscess wall, including the gliotic layer, while TGFβ reactivity was most intense at the site of active fibrogenesis.

Fig. 1 **a** Early brain abscess immunostained for bFGF. The wall is composed of granulation tissue infiltrated with leukocytes. The fibrin layer lining the abscess center (*top*) and the leukocytes beneath are heavily labeled with bFGF. **b** Early brain abscess immunostained for GFAP to show horizontally oriented reactive astrocytes beneath the granulation tissue layer. **c** Early brain abscess immunostained for GFAP to serve as negative control for bFGF. Leukocytes and blood vessels are not stained. **d** Early brain abscess immunostained for bFGF to show strong reactivity in neutrophils and monocytes, while lymphocytes are not stained. **e** Early brain abscess immunostained for NGF to show moderate reactivity in neutrophils and large clumps of reaction product in macrophages. **f** Early brain abscess immunostained for PDGF to show mild reactivity in leukocytes and stronger reactivity in macrophages. **a**, **b** × 58; **c–f** × 438 (*bFGF* basic fibroblast growth factor, *GFAP* glial fibrillary acidic protein, *NGF* nerve growth factor, *PDGF* platlet-derived growth factor) ▶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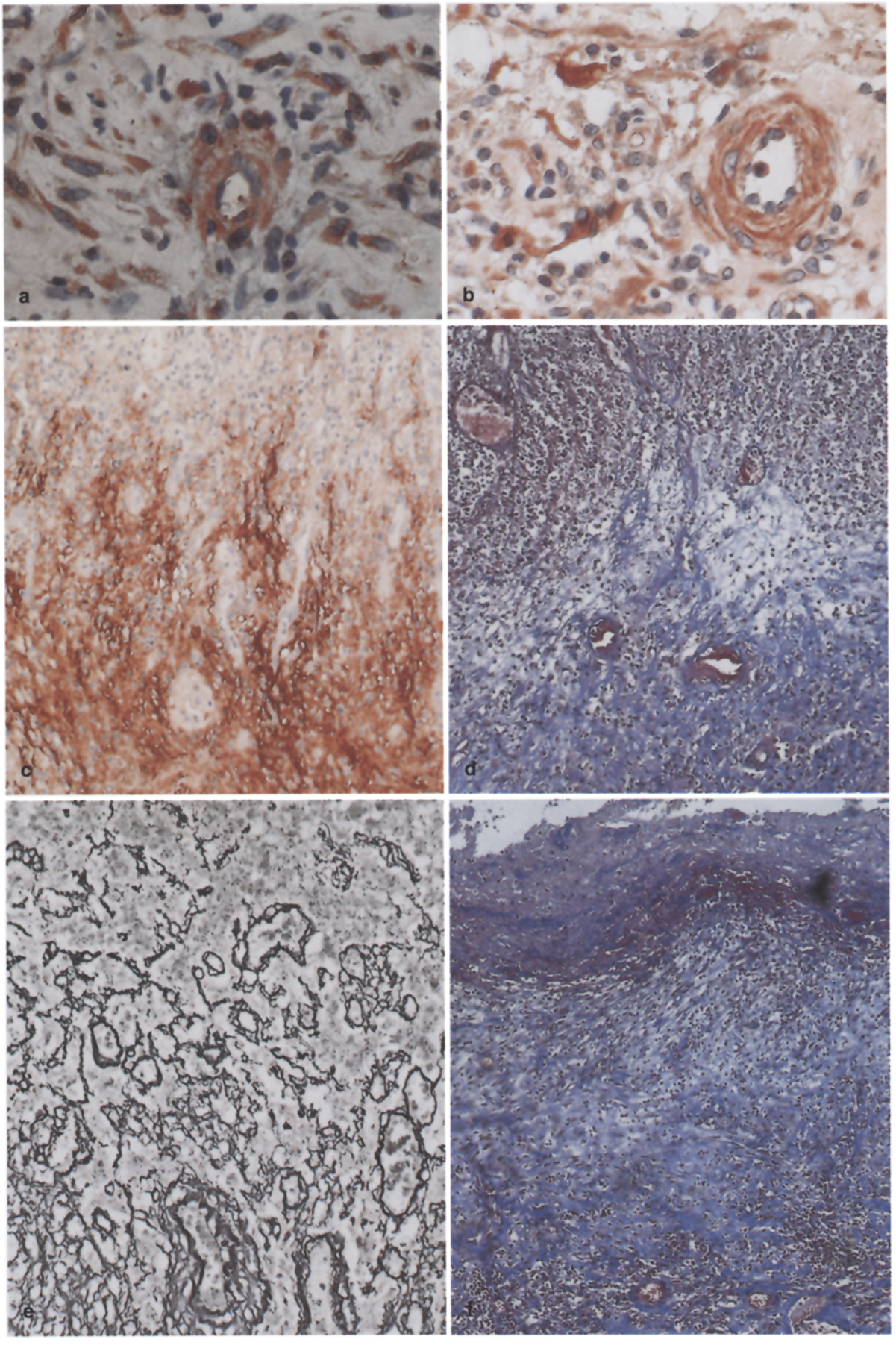
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Chronic abscess

One case had a 1-year history of persistent brain abscess and *Streptococcus viridans* was obtained on bacterial culture. This multiloculated abscess had a necrotic center surrounded by a thick collagenous mesodermal layer and an outer gliotic zone (Fig. 2f). The number of leukocytes and proliferating capillaries were markedly decreased. There was a general decrease in cellular expression of bFGF, NGF and PDGF, although TGFβ staining in ECM remained strong. The reactive astrocytes in the outermost gliotic zone still showed moderate intracellular NGF and PDGF activity. In Table 1, the intensity of growth factor expression by various cells and present in the matrix was arbitrarily represented by gradings of +, ++ and +++. The neuronal changes can not be assessed, as neurons were not included in any of the surgical specimens.

Table 1 Relative intensity of growth factor immunoreactivity in various cells and matrix in brain abscess (*bFGF* basic fibroblast growth factor, *NGF* nerve growth factor, *PDGF* platlet-derived growth factor, *TGFβ transforming growth factor-β, ECM* extracellular matrix)

Cell type	bFGF	NGF	PDGF	TGFβ
Neutrophil	+++	++	+	−
Monocyte/ macrophage	+++	++	++	−
Endothelial cell	+	+++	+++	−
Fibroblast	+	++	+	−
Astrocyte	+	+++	+++	−
ECM[a]	−	++	−	+++
Fibrin[b]	+++	+++	+++	−

[a] ECM in abscess wall
[b] Fibrin: fibrin/fibronectin clot in abscess center

◀ **Fig. 2** **a** Evolving brain abscess immunostained for NGF to show strong reactivity in vascular wall and in reactive astrocytes. **b** Evoloving brain abscess immunostained for PDGF to show strong reactivity in vascular cells and reactive astrocytes. **c** Evolving brain abscess immunostained for TGFβ to show diffuse ECM deposits and extension along blood vessels into the abscess center (*top*). **d** Evolving brain abscess stained with trichrome stain to shown perivascular collagen deposits (*blue*) extending into the abscess center (*top*). The collagen deposits correspond to that of TGFβ. **e** Evolving brain abscess stained with Wilder's reticulum stain to show perpendicularly oriented capillaries growing into the abscess center (*top*). **f** A chronic brain abscess stained with trichrome to show dense collagen deposits in the fibrotic wall. **a**, **b** × 175; **c**–**e** × 58; **f** × 28 (*ECM* extracellular matrix, *TGFβ transforming growth factor-β*)

Discussion

Expression of bFGF, NGF and PDGF by leukocytes

The production of bFGF, NGF, PDGF, TGFβ and cytokines by macrophages has been demonstrated by in vitro studies [39]. However, little attention has been paid to the expression of growth factors by infiltrating leukocytes in the wound. Previous autoradiographic study on NGF production in injured peripheral nerve has shown [^{35}S]mRNA granules in the proximal stump at the wound and throughout the length of distal segment [23]; the identity of cells expressing the NGF at the wound was not clear.

Our recent studies have shown NGF and bFGF staining in infiltrating leukocytes of many types of acutely injured tissues, including skeletal muscle, peripheral nerve, brain infarct and brain abscess. The possibility of a non-specific binding appears unlikely as adequate blocking procedure and negative controls have been used. As lymphocytes and plasma cells in the abscess wall were not stained for these growth factors, we consider the growth factor expression in neutrophils and monocytes/macrophages to be specific.

In non-infectious brain lesions such as ischemic infarct, the number of exudated leukocytes is small and they express modest amount of bFGF immunoreactivity [34]. In brain abscess, there is a continued influx of neutrophils and monocytes; the leukocytes and macrophages expressed strong NGF and bFGF immunoreactivities. These findings suggest that the expression of growth factors by inflammatory cells may be activated by cytokines and products of infection [19]. Alternatively, the growth factors manifested on neutrophils may be the result of a passive adsorption or phagocytosis of growth factors present in the environ of the brain abscess. These questions await future tissue culture and in situ hybridization analysis.

Expression of bFGF, PDGF, NGF and TGFβ by non-neural cells

The vascular cells, fibroblasts and astrocytes exhibited mild to strong immunoreactivities for bFGF, PDGF and NGF during the proliferative phase. Although TGFβ was not demonstrated within leukocytes and mesenchymal cells, a strong and diffuse TGFβ staining was demonstrated in the ECM of the abscess wall during the stage of fibrogenesis.

The role of bFGF in angiogenesis, gliosis and fibrosis

FGF are multifunctional polypeptides capable of stimulating the proliferation of fibroblasts, vascular endothelial cells, glial cells, Schwann cells, and muscle cells [18, 22, 36] and supporting the growth and survival of CNS neurons in vitro [47]. bFGF has been shown to be a morphogen, as it modulates the synthesis of ECM com-

ponents including fibronectin, laminin, collagen and proteoglycans [22, 36]. bFGF has been linked to angiogenesis in vivo and is considered to play a central role in tumor growth [25] and wound healing in a variety of tissues including the brain [1, 9, 12]. High levels of bFGF have been found in pituitary gland (350–600 μg/kg) and kidney (200 μg/kg), while brain contains 35–50 μg/kg of bFGF [22]. In normal brain, bFGF has been localized in astrocytes [21] and in neurons of the cerebral cortex, thalamus, hypothalamus, striatum, septum, hippocampus, amygdala, red nucleus, central gray of the midbrain, cerebellar nuclei, reticular formation, cranial motor nuclei and spinal cord [37].

There have been few detailed histological studies on the cellular localization of bFGF in diseased brains. In one study, local brain injury was created by suctioning a 4×6 mm piece of cerbral cortex through a glass pipette and the brains were removed 1 week later for study [16]. A mark increase of bFGF immunoreactivity was observed in reactive astrocytes at the borders of the lesion [16]. It is not known whether infiltrating leukocytes also expressed bFGF since leukocytic exudation is limited to the 1st week in uncomplicated wounds. In another study, an electrolytic lesion of the entorhinal cortex is followed within 2 days by increased bFGF immunoreactivity in reactive astrocytes and in ECM in the outer molecular layer of the ipsilateral dentate gyrus and no mention was made of the changes at the wound site [21].

In a recent study, we have demonstrated enhanced expression of bFGF in neurons adjacent to ischemic brain infarct followed within a day by glial and vascular proliferation in the same area [34]. The proliferative astrocytes and endothelial cells in turn expressed weak to moderate bFGF activity [34]. Although neurons were not included in the present human surgical material, our study on experimental brain abscess did not show enhanced neuronal bFGF expression (unpublished data). These findings suggest that in brain abscess, growth factors responsible for the angiogenesis, gliosis and fibrosis may be derived from infiltrating leukocytes and sustained by growth factors produced by the proliferating non-neural cells on an autocrine basis.

The role of PDGF and TGFβ

PDGF and TGFβ share certain common properties. Both are present in relatively high levels in platelets and both are produced by activated monocytes/macrophages [2, 3]. PDGF is present in astrocytes of normal brain; PDGF A and B chain genes are widely distributed in CNS neurons during development and maturity [51]. TGFβ messenger RNA is ubiquitously present in various normal and transformed cells and the amount appears to be correlated with mitotic activity [13].

PDGF and TGFβ are multifunctional proteins; both are chemotactic for neutrophils, monocytes and fibroblasts [15, 41, 46] and both are mitogens for fibroblasts and glial cell [14, 40]. TGFβ has dual properties and could be either growth stimulatory or growth inhibitory depending on the cell type. In a number of systems, the bioactivity of bFGF can be positively or negatively modulated by TGFβ. TGFβ inhibits the angiogenic effect of bFGF [4] and stimulates the synthesis of collagen, fibronectin and proteoglycans [11, 24, 44]. The appearance of TGFb in ECM during the stage of fibrogenesis in brain abscess demonstrated in the present study is in keeping with its important role in the modulation of cell growth and matrix formation.

The role of ECM

Exudation and deposition of fibrin/fibronectin commonly occurs in wound and in abscess. The major role of the fibrin/fibronectin clot appears to be the promotion of growth and migration of endothelial cells, fibroblasts and Schwann cell/axon [32, 33]. The demonstration of bFGF, PDGF and NGF in the fibrin layer of the brain abscess suggests binding of these factors to the fibrin clot and the macromolecular matrix thus formed may provide an optimal microenvironment for the directional growth of non-neural cells during wound healing.

During the evolution of the abscess wall, growth of capillaries and perivascular deposition of connective tissue matrix was noted. bFGF and TGFβ share the common property of binding to matrix components such as proteoglycans, although each has different biological properties. On the whole, binding of bFGF and TGFβ in ECM and their ability to promote and inhibit cell proliferation and fibrogenesis suggest unique synergistic functions for these molecules in the formation of the abscess wall.

The role of NGF

NGF is produced in large amount by male mouse salivary glands [28] and in limited amount by glial cells, Schwann cells, target cells (fibroblasts, smooth muscle cells, endothelial cells) and macrophages [5, 30, 42]. NGF is thought to plays a central role in developmental nerve growth, nerve regeneration and possibly degenerative diseases in the brain [20, 23, 42, 49].

Evidence for associations between NGF, wound healing and immunity have just begun to emerge. The production of NGF by astrocytes is promoted by interleukin-1 and tumor necrosis factor [19]. These cytokines are known to be products of activated monocytes and could explain the strong expression of NGF by the non-neural cells in brain abscess. The NGF in turn may mediate many steps in wound healing and defense mechanisms. For instance, NGF is chemotactic for neutrophils [6]. It activates plasminogen and the classical complement cascade [26], induces fibrinolysis and accelerates wound healing [29]. The possible associ-

ation of NGF with chronic inflammation and immunological disorders is suggested by the fact that NGF induces growth and differentiation of B lymphocytes [38]. Increased NGF has been found in cerebrospinal fluid of patients with multiple sclerosis [27] and in serum of patients with systemic lupus erythematosus [7].

Conclusion

Growth response in wound healing is likely to be mediated by a network of cytokines and growth factors present at the wound. In brain abscess, bFGF and PDGF elaborated by prolonged exudation of leukocytes, platelets and activated macrophages may be responsible for the proliferation of capillaries, fibroblasts and glial cells. The bFGF and TGFβ may act synergistically in the deposition of matrix and formation of the mesodermal layer. It remains to be established whether the NGF and bFGF demonstrated by immunohistochemistry in infiltrating neutrophils and monocytes represent a de novo synthesis or a passive adsorption of growth factors present in the wound milieu.

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