

PERITONEAL ADHESIONS: They Appear to be Cellular, Innervated, and Vascularized Entities

Presence and Distribution of Sensory Nerve Fibers in Human Peritoneal Adhesions
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Peritoneal adhesions are bands of fibrous tissue that join abdominal organs to each other or the abdominal wall. Adhesions develop rapidly after damage to the peritoneum during surgery, infection, trauma, or irradiation. Postoperative adhesion formation occurs in 93% to 100% of patients undergoing laparotomy, leading to complications such as intestinal obstruction and infertility in women. Adhesions have also been implicated as a cause of chronic abdominopelvic pain, and many patients have been relieved of their symptoms after adhesiolysis. Chronic pelvic pain accounts for up to 25% of all gynecologic visits, 30% to 50% of all diagnostic laparoscopic procedures, and approximately 5% of hysterectomies. In financial terms, the annual cost of resources for the diagnosis and treatment of women with chronic pelvic pain in the United Kingdom is approximately £600 million, and therefore the role of adhesions in pain etiology should be addressed.

It has been proposed that peritoneal adhesions indirectly cause pain by restricting organ mobility or expansibility and thus stimulating stretch receptors in the smooth muscle of adjacent organs or the abdominal wall. However, mapping studies of reported pain using microlaparoscopic techniques showed that 80% of patients with significant pelvic adhesions reported tenderness when these structures were probed, suggesting that these structures can generate pain stimuli. The presence of nerve fibers in human pelvic and abdominal adhesions supports this theory. The aim of the present study was to characterize the type of nerve fibers found in human peritoneal adhesions using histologic, ultrastructural, and immunohistochemical techniques and to relate the findings to the location, size, and estimated age of the adhesions and clinical parameters such as reports of chronic pelvic pain. Nerve fibers were identified using antibodies directed against synaptophysin, a protein of synaptic vesicles, and the neuropeptides calcitonin gene-related peptide (CGRP), expressed by sensory nerves, and substance P, present in pain-conducting fibers. Fibers expressing vasoactive intestinal peptide (VIP), a marker for cholinergic sympathetic nerve fibers, and tyrosine hydroxylase (TH), an intermediary enzyme in catecholamine synthesis of adrenergic nerve fibers, were also identified.

RESULTS

Peritoneal adhesions were heterogenous in appearance but consisted mainly of vascularized collagenous bands lined by adipose tissue. Some adhesions from the upper abdominal cavity showed clear zones of demarcation between the fatty and fibrous tissues, whereas pelvic adhesions appeared more fibrous.

Nerve fibers were clearly identified in all peritoneal adhesions examined immunohistochemically and appeared more abundant in the abdominal adhesions versus the pelvic adhesions. Fibers were immunoreactive for all the neuronal markers examined (synaptophysin, CGRP, substance P, VIP, TH), irrespective of site, size, and estimated age of the adhesion or the surgical history of the patient. Adhesions from the five patients without a history of chronic abdominopelvic pain also displayed the sensory nerve markers CGRP and substance P. Small bundles of axons, as well as single axons with a distinct beaded or varicose appearance, were identified.

Most nerve fibers colocalized with blood vessels, as shown by dual staining, and were generally arranged parallel to the longitudinal axis of the adhesion. Some nerve fibers were found in the interstitium and in the adventitia of the blood vessels. This pattern of staining was similar for all the neuronal markers, except that TH-immunoreactive axons were fewer in the interstitium but more abundant in the adventitia of blood vessels. Some fibers branched from the longitudinal fibers and traversed the adhesions independent of the blood vessels. This finding was confirmed by acetylcholinesterase histochemistry. On ultrastructural examination, nerves were composed of both myelinated and thinner nonmyelinated fibers with accompanying Schwann cells. The nerves had a random orientation with respect to the peritoneal surface.

DISCUSSION

In this study, all the peritoneal adhesions examined contained nerve fibers. The fibers were immunoreactive for all the neuronal markers assessed, irrespective of the site of the adhesion, its size, or its estimated age. Past surgical intervention, inflammation, or reports of chronic pelvic pain did not influence the proportion or type of nerve fibers found.

Substance P-immunoreactive and CGRP-immunoreactive nerve fibers were observed throughout the samples, and because these peptides are abundant in sensory nerves, it is likely that these fibers are part of a sensory pathway. Moreover, the small-diameter nonmyelinated fibers, shown by electron microscopy, could be C or A-delta fibers, both known to be involved in the conduction of pain stimuli.

The association of nerve fibers with blood vessels, as shown by dual immunolocalization and acetylcholinesterase histochemistry, suggests that angiogenesis may play an important role in regulating the growth of nerve fibers into adhesions. Hill et al. found that the reinnervation of arterial smooth muscle and intrinsic neurons of the gut, after disruption of their nerve supply, was predominantly by sympathetic fibers (TH- and VIP-immunoreactive) regenerating from the interrupted paravascular nerve bundles. Further, after ileal transplantation, regenerating fibers expressing a number of neuronal markers such as CGRP, substance P, and TH, extend toward the anastomotic site from paravascular fibers in the mesentery. In the developing adhesion, blood vessels appear 3 days after injury. They may therefore guide nerve growth through the release of trophic factors and the deposition of extracellular matrix tracts. The finding that some nerve fibers appeared to be independent of blood vessels suggests that their growth was influenced by additional stimuli, such as chemotactic inflammatory mediators, or inhibited by dense fibrotic areas within the adhesions.

The effect of innervation on adhesion function is not known, but neuropeptides released by nerves are thought to be involved in a number of processes, including the

control of blood flow and the regulation of neurogenic inflammation. Both neurokinin A and substance P have been shown to stimulate fibroblast and arterial smooth muscle cell proliferation, and neurokinin A also induces fibroblast chemotaxis. Neuropeptides such as CGRP and substance P are thought to be essential for normal wound healing: denervated wounds heal more slowly and have a reduced inflammatory infiltrate compared with controls. In terms of the peritoneum, it has been postulated that increasing the intensity of neural stimuli, through stretch or distension of viscera, may lead to antidromic release of neuropeptides, resulting in the recruitment of peripheral neural sensory branches and the release of inflammatory mediators. Hence, repeated distortion and stretching of adhesions may lead to the release of neuropeptides and so influence fibroblast activity and modulate the deposition of connective tissue during adhesion maturation.

Nerves in the adhesions may also be involved in the occurrence of chronic pelvic pain. This study is the first demonstration of sensory nerve fibers, including those that may generate pain stimuli, in human peritoneal adhesions. However, five patients reported no abdominopelvic pain 3 to 6 months before surgery, even though their adhesions also contained nonmyelinated axons and fibers immunoreactive for the sensory neuronal markers present in painconducting fibers. This suggests that the presence of sensory nerves in adhesions does not necessarily involve chronic abdominopelvic pain. These nerves may be nonfunctional or require a series of inducing stimuli to transmit pain sensations, as in the visceral peritoneum. The number of A-delta and C primary afferents supplying the viscera is small in comparison with the number of fine afferents in somatic nerves to the abdominal wall. These visceral afferents, unlike somatic fibers, probably have neither nociceptive nor high-threshold, specialized nerve endings that, when stimulated, specifically result in the sensation of pain. Instead, they terminate in mechanoreceptors that have the capacity of a graded response that depends on the intensity of the stimulus. Visceral pain is thought to reflect an abnormal involvement of the neural mechanisms usually concerned with the mediation of reflexes and amorphous sensations, which with added mechanical or chemical stimuli respond with increased intensity and are therefore perceived as painful stimuli. A similar mechanism may exist in human adhesions, where a combination of distention, hypoxia, and inflammation may result in the stimulation of sensory fibers in the adhesions and the perception of chronic abdominopelvic pain. In addition to this direct role, adhesions may cause abdominopelvic pain by restricting the mobility of internal organs and thus stimulating preexisting stretch-sensitive fibers in the muscle of viscera.

In conclusion, this study has shown the presence of sensory nerves within all the human peritoneal adhesions examined. Although pain physiologic studies were not conducted, it is possible that the thin nonmyelinated fibers observed conduct pain stimuli. However, not all patients in this study experienced chronic pelvic pain; therefore, although all adhesions may be able directly to give rise to pain sensations, there are likely to be other factors to consider, in addition to the innervation, such as peritoneal pathology, organ mobility, and psychosomatic manifestations.

Human peritoneal adhesions are highly cellular, innervated, and vascularized Sarah E. Herrick , Steven E. Mutsaers , Peter Ozua , Hassan Sulaiman , Abdul Omer , Paul Boulos , Martyn L. Foster , Geoffrey J. Laurent. Journal of Pathology Early View. Vol. 192 Issue 1, pp. 67-72. 26 Jun 2000 (online). © 2008 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.

Peritoneal adhesions are a major complication of healing following surgery or infection and can lead to conditions such as intestinal obstruction, infertility, and chronic pain. Mature adhesions are the result of aberrant peritoneal healing and historically have been thought to consist of non-functional scar tissue. The aim of the present study was to analyse the cellular composition, vascularity, and extracellular matrix distribution of human peritoneal adhesions, to determine whether adhesions represent redundant scar tissue or are dynamic regenerating structures. Furthermore, the histological appearance of each adhesion was correlated with the clinical history of the patient, to determine whether maturity or intraperitoneal pathology influences adhesion structure. Human peritoneal adhesions were collected from 29 patients undergoing laparotomy for various conditions and were prepared for histology, immunocytochemistry, and transmission electron microscopy. All adhesions were highly vascularized, containing well-developed arterioles, venules, and capillaries. Nerve fibres, with both myelinated and non-myelinated axons, were present in adhesions from nearly two-thirds of the patients, with increased incidence in those with a malignancy. Approximately one-third of the adhesions contained conspicuous smooth muscle cell clusters lined by collagen fibres of heterogeneous size. Adipose tissue was a consistent feature of all the adhesions, with some areas displaying fibrosis. There appeared to be no correlation between the estimated maturity or site of each adhesion and its histological appearance. However, intraperitoneal pathology at the time of surgery did influence the incidence of some histological features, such as the presence of nerve fibres, clusters of smooth muscle cells, and inflammation. This study challenges previous concepts that adhesions represent non-functional scar tissue and clearly demonstrates that established adhesions are highly cellular, vascularized, and innervated, features more consistent with dynamic, regenerating structures. Copyright © 2000 John Wiley & Sons, Ltd.