



Cytogenetic Analysis of Several Pseudomyxoma Peritonei Lesions Originating from a Mucinous Cystadenoma of the Appendix

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ABSTRACT: Epithelial proliferative lesions of the appendix are rare and have never been studied cytogenetically. We present the chromosomal banding analysis of four successfully short-term cultured samples from pseudomyxoma peritonei lesions originating from a cystadenoma of the appendix. All four samples contained clonal chromosome abnormalities. In three of them, the clone 46,XX,der(6)?del(6)(q16q21)?del(6)(q27) was found, whereas a clone with the karyotype 46,XX,t(2;17)(p21;p13),t(6;12)(p21;q13),t(12;15)(q24;q15) was detected in the fourth sample. Our findings support the view that pseudomyxoma peritonei originates by spreading from a primary mucinous neoplasm of an intraperitoneal organ rather than through mucinous metaplasia or multifocal primary neoplastic transformation of the peritoneum. © Elsevier Science Inc., 1997

INTRODUCTION

Epithelial proliferative lesions of the appendix are rare. Relatively most common among them are mucosal hyperplasia, mucinous cystadenoma, and mucinous cystadenocarcinoma [1]. To the best of our knowledge, none of these neoplasms has been studied cytogenetically. Therefore, the chromosomal changes important in their development are unknown.

Pseudomyxoma peritonei is a clinical entity in which the peritoneal surfaces are covered by mucus-producing lesions. The condition is usually thought to arise through spreading from a primary mucinous neoplasm of an intraperitoneal organ, often the appendix or ovary [2]. Recently, Vasilev et al. [3] were the first to describe karyotypic abnormalities in a peritoneal implant presumably originating from an ovarian mucinous cystadenocarcinoma. In this report, we describe the chromosomal aberrations found in several pseudomyxoma peritonei foci in a patient who had a cystadenoma of the appendix.

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MATERIALS AND METHODS

Case Report

A 44-year-old man sought medical care in September 1995 because of an unpleasant sensation in the right part of the abdomen and a movable mass in the right fossa iliaca. An enlarged appendix was found by laparoscopy. There were ascites and peritoneal tumor nodules in all four abdominal quadrants. The clinical diagnosis was pseudomyxoma peritonei. The appendix was removed and the histopathologic analysis revealed a mucinous cystadenoma with atypia. There was no tumor infiltration but in several places, mucus was oozing out of the appendiceal wall. Atypical epithelial cells were found in the mucus. In November 1995, a radical peritonectomy with cholecystectomy, ileocecal resection, and five days postoperative intraabdominal chemotherapy was attempted with curative intent.

Cytogenetic Techniques

Peritoneal tumor lesions from the upper left quadrant (sample 1), pelvis (sample 2), left colon (sample 3), right colon (sample 4), and upper right quadrant (sample 5) were obtained during surgery and brought under sterile conditions to the cytogenetics laboratory. The samples were disaggregated mechanically as well as enzymatically overnight with collagenase (450 U/ml), hyaluronidase (0.2 mg/ml), and neuraminidase (2 U/ml). The resulting cells were plated out in 25 cm² Primaria flasks and Vitrogen-coated slide-flasks. The cultures were fed an appropriate medium that facilitates epithelial growth [4] and harvested after 8 to 15 days. Chromosome preparations were made as described by

Table 1 Karyotypic data on the successfully analyzed pseudomyxoma peritonei samples

Sample	Karyotype
1	46,XX,t(2;17)(p21;p13),t(6;12)(p12;q13),t(12;15)(q24;q15)[7]/46,XX[13]
2	46,XX,der(6)?del(6)(q16q21)?del(6)(q26)[7]/46,XX[8]
3	46,XX,der(6)?del(6)(q16q21)?del(6)(q26)[1]/46,XX[4]
4	46,XX,der(6)?del(6)(q16q21)?del(6)(q26)[2]/46,XX[6]

Pandis et al. [5]. Some cultures in slide-flasks were harvested in situ as described by Mandahl [6]. G-banding was obtained with Wright stain. The clonality criteria and the description of karyotypes followed the recommendations of the ISCN [7].

RESULTS AND DISCUSSION

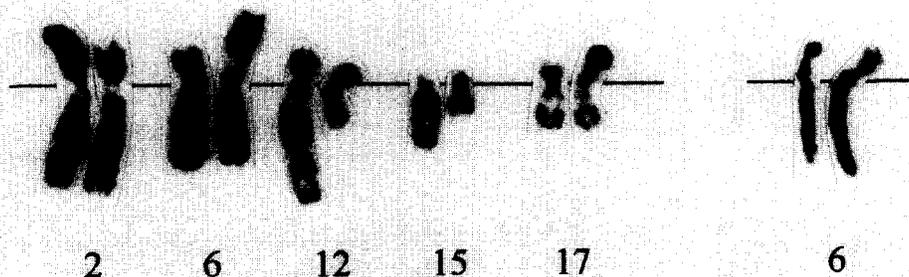
All samples, except the one obtained from the upper right abdominal quadrant, were successfully cultured and could be shown to contain cells with clonal chromosomal abnormalities (17 of 48 metaphase cells; Table 1, Fig. 1). Some uncertainties regarding the loss of 6q material seen in 10 mitoses should be mentioned. We are confident that one 6q in these cells is rearranged and shorter than its normal counterpart, but had to stipulate the presence of two separate small deletions to obtain a derivative chromosome with the observed banding pattern. Attempts to paint with chromosome-specific probes did not yield additional information.

The pathogenesis of pseudomyxoma peritonei has generally been attributed to spillage of material from a primary mucinous neoplasm, usually located in the appendix or ovary [2, 8]. On the other hand, some investigators have suggested that the peritoneal tumors arise as the result of mucinous metaplasia of the peritoneum in response to the presence of ascitic fluid [9, 10], or that multifocal, primary, mucinous neoplastic transformation of the peritoneum occurs [11]. Because metaplasia is a reversible process,

it is highly unlikely to involve stable, clonal genetic changes. If the sampled lesions arose de novo as independent, primary neoplasms of the peritoneum, then one would expect them to be genetically abnormal, but presumably so that each lesion had a different karyotype. However, the cytogenetic analysis in the present case revealed the same chromosomal pattern in three of four widely separated peritoneal sites, a result that strongly favors the first of the three above-mentioned pathogenetic mechanisms. This is of course further supported by the histopathologic finding of atypical epithelial cells in the mucus making their way through the discontinuous appendiceal wall.

The cells carrying the 6q rearrangement (Fig. 1) were present in samples taken from the pelvis and both the left and right colon. Most likely, this chromosomal abnormality was present in the mucinous cystadenoma of the appendix already before spreading occurred. A cytogenetically unrelated clone with three apparently balanced translocations (Fig. 1) was found only in the mucinous lesion from the upper left abdominal quadrant. That this clone too must have been present in vivo is certain because cells with the same aberrations were found in independent short-term cultures. We have recently demonstrated in breast carcinomas that different domains of epithelial tumors may contain cytogenetically abnormal but karyotypically unrelated cell populations [12, 13]. If such clonal heterogeneity exists also in appendiceal neoplasms, as our findings indicate, then it would seem that, for purely stochastic reasons, different clones predominated in tumor material leaving the ap-

Figure 1 Partial karyotypes illustrating the aberrant clones present in the pseudomyxoma peritonei lesions. The changes t(2;17)(p21;p13), t(6;12)(p21;q13), and t(12;15)(q24;q15) (left) were found in sample 1, whereas a der(6)?del(6)(q16q21)?del(6)(q27) (left chromosome in the homologue pair to the right) was found in samples 2 to 4.



pendix through different parietal discontinuities. This also presupposes that the rupture of the dilated appendix was brought about by mechanical stress of mucus in its lumen rather than any preferential ability of particular tumor subpopulations to infiltrate the organ's wall.

This report presents the first karyotypic data on appendiceal tumors. The only previously published cytogenetic study of pseudomyxoma peritonei [3], which in that case originated from an ovarian mucinous cystadenocarcinoma with low malignant potential, detected a clone with the pseudodiploid karyotype 46,XX,del(1)(p21p31),t(2;6)(q35;p21). Beyond the relative karyotypic simplicity found in both cases, the only similarity with the case we describe appears to be the involvement of chromosomal band 6p21. It would be premature to speculate that the rearrangements of this particular genomic region play any specific role in mucinous tumor differentiation or in the spreading of these tumors to the peritoneum; more data are obviously needed before even educated guesses about the genetic pathways taken by these neoplasms can be formulated.

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