HYDROGEL AND BREAST CANCER: CAUSALITY OR COINCIDENCE?

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ABSTRACT

We present a case of 36-year old woman who volunteered for breast augmentation with a polyacrylamide hydrogel at the age of 21. For the next decade she suffered a multitude of complications with appearance of irregular, firm lesions in both her breasts and axillae. Several surgical procedures were performed aiming the removal of the hydrogel. Billateral subcutaneous mastectomy was performed; mammary implants were placed beneath the pectoral muscles. In December 2012, the patient came to our hospital complaining of subcutaneous induration in the left lateral breast. Data from the ultrasound was interpreted as granulation tissue and the lesion was subsequently extirpated. Because of prior history and image studies support, the clinical team did not have a malignant disease in consideration. The final diagnosis of the material submitted for histological investigation was high grade invasive ductal carcinoma with extensive high grade in- situ ductal cancer. The patient was advised to undergo further oncologic surgery appropriate for the diagnosis.

With the background for hydrogel application in the breasts, early detection of breast cancer that emerged later was made difficult and she missed the correct oncologic approach to her disease.

Key words: *polyacrylamide hydrogel, complications, breast cancer.*

INTRODUCTION

Polyacrylamide hydrogel was first manufactured in Ukraine in the late 1980s and advertised as easily accessible and affordable biomaterial for "breast augmentation without surgery". The hydrogel is nontoxic, stable, nonresorbable sterile watery gel consisting of approximately 2.5% cross-linked polyacrylamide and nonpyrogenic water. Some authors have concluded that hydrogel is highly biocompatible, diffusion and migration resistant (4). Recently, however, there is a steady increase in the number of reports commenting on early and late complications (1-3, 5-10), including a few cases of breast cancer after application of hydrogel in breasts without previous surgery (2).

CASE PRESENTATION

In 1997**,** a woman at the age of 21 at that time, was one among the first in Bulgaria to have both her breasts augmented with hydrogel. Medical indications for the procedure were absent. With due time, she noticed small irregular lumps in both breasts, hard to the touch. Similar, though painful, indurations were palpated by her in axillar regions. Gradually, these lumps increased their size and in 2004, she turned up at the Clinic of Plastic Surgery in our hospital. At clinical examination, her breasts were found grossly asymmetric, the left submammary fold was 1 cm lower than right. Moderately firm, irregularly shaped lesions were noted upon palpation; both axillae were found to contain similar abnormal areas, mimicking enlarged lymph nodes. Laboratory data was

within normal range. She was subsequently referred for elective surgery. Both breasts were inspected, each contained two separate collections of hydrogel- one superficial between skin and major pectoral muscle; the other beneath the major pectoral muscle, infiltrating the anterior serrated, the minor pectoral muscles, intercostal muscles and the proximal part of rectus abdominis. Two "channels" were found to drain hydrogel to axillar fat tissue, where further collections were found within cystic spaces. Normal breast tissue was largely replaced by connective tissue and innumerous smaller light-yellow hydrogel deposits with jelly-like consistency. Billateral subcutaneous mastectomy was performed; mammary implants were placed beneath the pectoral muscles.

Histology revealed multiple collections of acellular, homogenous material that stained blue-violet with H&E, corresponding to hydrogel. Some deposits were rimmed with macrophages and walled off by delicate fibrous tissue, foreign-body type multinucleated giant cells were dispersed within and around the hydrogel (**Fig. 1A, B**). Hygrodel was found to have spilled between basic breast structures - surrounding ducts and acini (**Fig. 1C**); further sections revealed hydrogel permeating striated muscles (**Fig. 1D**).

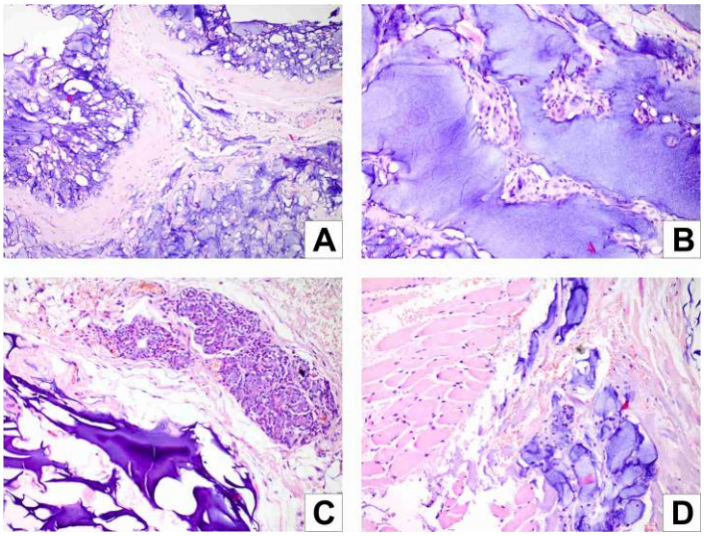

Fig. 1. H&E. **A:** hydrogel deposits rimmed with macrophages and walled off by delicate fibrous tissue. **B**: foreign-body type multinucleated giant cells dispersed within around the hydrogel. **C**: hygrodel spilled between basic breast structures. **D:** hyrogel permeating striated muscles.

She was discharged from our clinic and was lost to follow-up for the next 8 years and finally re-appeared in late 2012 when she reported to have had a few small surgical interventions aimed at removing additional hydrogel from both breasts. Her current visit was remarkable for the presence of subcutaneous induration in the left lateral breast, slightly tender to palpation and covered by atrophic skin. No enlarged lymph nodes were found. Data from the ultrasound was interpreted as granulation tissue and the lesion was subsequently extirpated. Because of prior history and image studies support, the clinical team did not have a malignant disease in consideration.

The material sent for histological examination was a whitish, firm soft tissue plaque – 9/5/2 cm, with a thin rim of fat tissue. The cut surface was granular (**Fig. 2A**). Representative samples were stained with H&E. These revealed that the predominant part of the tissue present was actually high grade in situ ductal carcinoma with comedo necrosis (**Fig. 2B**). Within the stroma, small areas with irregularly shaped neo-tubules were seen, indicative for invasive carcinoma (**Fig. 2C**). In the periphery of the specimen, myriad of tumor emboli in vascular spaces were found (**Fig. 2D**).

Staining for myoepithelial cells was performed to differentiate the in situ and invasive component of the tumor: CD 10 (**Fig. 3A**) and Myosin heavy chain (**Fig. 3B**). Hormone receptor status - Estrogen (positive - **Fig. 3C**), Progesteron (positive - **Fig. 3D**) and HER-2 (negative) – was examined mostly in the tumor emboli because of the small amount of the invasive component. The final diagnosis was high grade invasive ductal carcinoma with extensive high grade in- situ ductal cancer. In the submitted material no trace of hydrogel was present. The patient was advised to undergo further oncologic surgery appropriate for the diagnosis. She preferred medical treatment abroad.

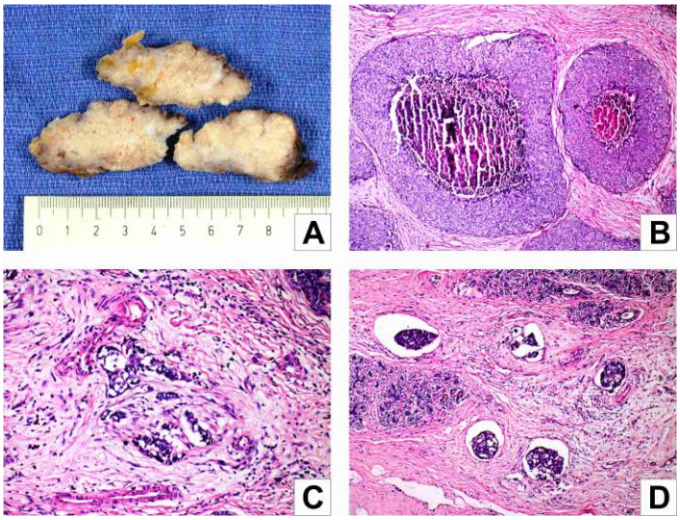

Fig. 2. A: gross specimen. **B**: high grade in situ ductal carcinoma with comedo necrosis (H&E). **C:** high grade invasive ductal carcinoma (H&E). **D:** tumor emboli in vascular spaces (H&E).

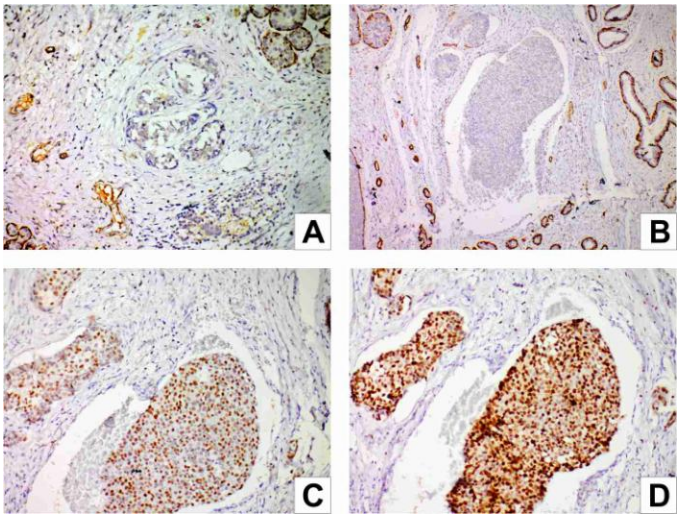

Fig. 3. Immunohistochemistry. **A**: CD10. **B:** Myosin heavy chain. **C:** Estrogen receptor. **D:** Progesteron receptor.

DISCUSSION

For centuries, women have desired to modify their bodies for a myriad of reasons with special accent on the breasts. In response, plastic surgeons have searched for an easy, painless, and safe

biomaterial for breast augmentation. Nonbiodegradable materials such as silicone was first introduced, gained popularity and widely used until many different complications, including foreign body reactions, were reported. This was followed by new generation of biodegradable materials such as collagen and hyaluronic acid that are still being used. Although these materials are considered much safer than nonbiodegradable materials, these injected fillers maintain their shape for only approximately 6 months. Polyacrylamide hydrogel was subsequently developed and has since gained international attention as a new, theoretically ideal, injectable and permanent filler. On the market, hydrogel products are offered under different brands and names: Interfall, Royamid, Formacryl, Aquamid, Amazing-gel, Evolution, and Outline in Europe and China. Christensen et al. based on their huge experience for more than 10 years and approximately 30 000 women, reported good results in augmentation mammaplasty using polyacrylamide gel injection and concluded that the gel is non toxic, well tolerated by the breast and does not give rise to severe pain, fibrosis, and capsular shrinkage (4). Meanwhile, several authors have reported complications such as indurations, palpable lumps, gel migration and loss of contour, hematoma, and subsequent infection associated with breast augmentation using this product (3, 7-10).

Since 1994, hydrogel has been used by some dermatologists and surgeons in Bulgaria, mostly in the private setting. A number of candidate patients have opted to undergo hydrogel injection for the different purposes, blinded by its simplicity ant the good immediate cosmetic result. After 10 years, D. Evstatiev – plastic surgeon who had never used hydrogel, reported his own observations in a series of 19 female patients with different complications, including displacement and migration in 8 patients, inflammatory reaction in 5 patients, partial necrosis of the skin in 2 patients, partial necrosis of the breast tissue in 9 patients, functional disruption in 17 patients, and pain in 11 patients (5, 6). All of these complications arose from 6 months to a few years after application of the hydrogel.

Another major complication that is underestimated appeared to be the often misleading results from physical and imaging studies of the breasts with prior hydrogel application. By palpation, differentiating breast tissue modified by hydrogel and other pathological process is extremely difficult and this diminishes the value of this routine method. Further more, imaging modalities like ultrasound, mammography and MRI have limited ability to visualize early, preclinical neoplastic changes. Once inserted, hydrogel seems to be really stubborn to remove. Attempts at compete, one-time removal usually fail and necessitate additional surgical interventions.

In 1996, shortly after hydrogel was introduced, the use of hydrogel in Bulgaria was legislatively forbidden. However, almost two decades later, clinical and pathological practices often witness the late complications of hydrogel.

2003 year a statement of International Agency for Research on Cancer declared Acrylamide to be probably carcinogenic to humans (1). However, sufficient data is still lacking in published literature to clarify the possible connection between hydrogel and breast cancer.

IN SUMMARY, we present a case of 36-year old female patient who volunteered for breast augmentation with a novel hydrogel product. For the next decade she suffered a multitude of complications with appearance of irregular, firm lesions in both her breasts and axillae. With this background, early detection of breast cancer that emerged later was made difficult and she missed the correct oncologic approach to her disease.

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