

## Histological Appearance of the Synovial Membrane after Treatment of Knee Osteoarthritis with Polyacrylamide Gel Injections: A Case Report

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### Abstract

Knee osteoarthritis (OA) caused by cartilage damage and synovitis is a painful disease, for which the only effective treatment today is total knee replacement. Polyacrylamide hydrogel (PAAG) is a synthetic non-degradable and non-toxic tissue filler, which allows host cell integration with formation of a scaffold of fibrous tissue inside the gel. A histo-pathological pilot study using this gel for intra-articular injection in rabbit and horse joints has shown that it forms an integrated layer within the upper part of the synovial membrane, and clinical studies of horse joints and human knee joints with OA has shown promising long-term results in pain reduction. It has therefore been the hope that this type of treatment could prolong the time leading up to total knee replacement more effectively than today. The current case report from one of the patients included in the clinical study mentioned above describes, for the first time in a human, how biopsies obtained during meniscectomy after 9 months display the same type of synovial augmentation as seen in horse joints with OA, and that the filler effect from the integrated gel persists in spite of areas with chronic synovitis and microscopic fibrosis.

**Keywords:** Treatment of knee osteoarthritis; Polyacrylamide integration; Histo-pathology

### Introduction

Knee osteoarthritis (OA) is a chronic, progressive disorder characterized by joint cartilage degeneration associated with concomitant changes in the synovium and subchondral bone metabolism. It is a common disabling disease characterized by knee pain and swelling due to cartilage damage and synovitis [1,2]. A variety of treatment options are available, of which intra-articular injection with steroid is still the most effective, albeit with transient effect [3]. Total knee replacement remains the only effective treatment for knee osteoarthritis today [4].

Polyacrylamide hydrogel (PAAG), Contura International, Soeborg, Denmark, is a synthetic non-degradable and non-toxic tissue filler product [5], which exerts its effect in vivo by allowing integration of host cells, initially macrophages and giant cells, who are later replaced by fibroblast-like cells [6,7]. These cells anchor the injected gel to the injection site by forming a scaffold of fibrous tissue inside the gel, which on the other hand shows an ongoing exchange of its 97.5% water molecules with those of the surrounding matrix [8].

A histo-pathological pilot study using this gel for intra-articular injection in rabbit and horse joints has shown that it forms an integrated layer within the upper part of the synovial membrane [7], and a clinical study of human knee joints with OA conducted during the past 5 years has shown promising long-term results in pain reduction [9], similar to those previously found in horse joints with OA [10]. Therefore, it has been the hope that this type of treatment could prolong the time leading up to total knee replacement more effectively than today. The current case report from one of the patients

included in the clinical study mentioned above describes, for the first time in a human, the histological findings in synovial biopsies obtained during surgery for meniscectomy nine months after the gel injection.

### Case Report

A 68-year old woman with a body mass index (BMI) of 30 was admitted for intermittent pain



**Figure 1:** MR-scanning photo. Moderate degenerative changes, predominantly laterally with severe displacement and degeneration of the left meniscus were described (Gildhoj hospital, Brøndby, Denmark).

and swelling of her left knee with instability and episodes of locking. Magnetic resonance imaging (MRI) and radiography showed signs of

arthrosis (Figure 1), and ultrasound examination showed degenerative changes with reduced joint space, osteophyte formation and sparse exudate, corresponding to Kellgren-Lawrence score 2 [11]. The only previous medical treatment had been non-steroid anti-inflammatory drugs with a slight analgetic effect.

Knowing about the PAAG pilot study through her job, the patient now chose injections with polyacrylamide gel as the next treatment approach.

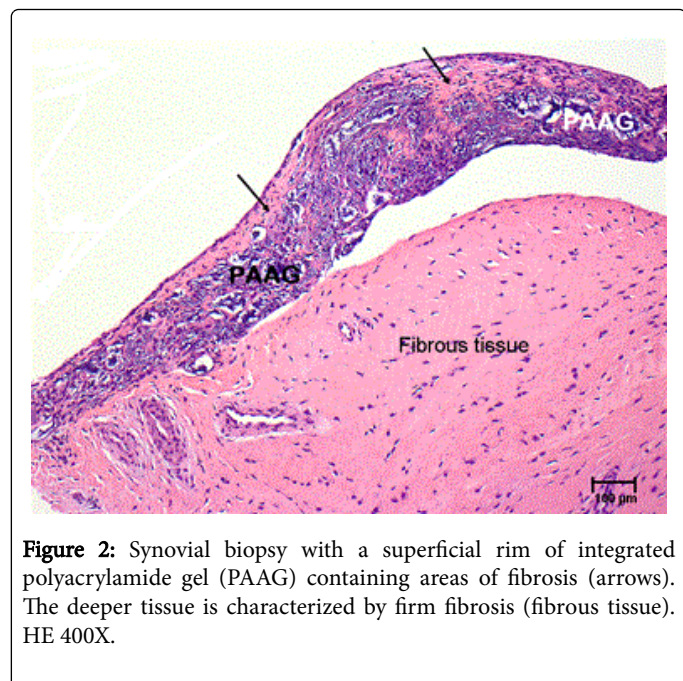
After having signed informed consent the patient received 2 ultrasound-guided intraarticular injections of polyacrylamide hydrogel (PAAG) (3 ml) with 1 month interval, each time preceded by a local anaesthetic (Carbocain 10 mg/ml, Astra-Zenica A/S).

Prophylactic peroral antibiotics (Moxifloxacin, 400 mg×1 and Azithromycin, 500 mg×1) were administered 2 h prior to each treatment. There was no inflammatory response, swelling or pain for the first week after the injection.

Nine months after the last gel injection the patient had no more pain or swelling, but she was still suffering from episodes of locking, which turned out to be due to a large lesion of the lateral meniscus.

Therefore, the meniscus was removed arthroscopically, the joint was rinsed, and with the patient's permission five biopsies at 2-8 mm in diameter, were obtained.

Routine hematoxylin and eosin (HE) histology showed four biopsies representing the synovial membrane and one containing fatty tissue only. All four biopsies from the synovium showed various degrees of PAAG-augmentation, which appeared as a blue gel lying as an integrated layer just beneath the surface cells of the synovial lining (Figures 2 and 3, PAAG), with a thickness varying from 100 to 350 µm.

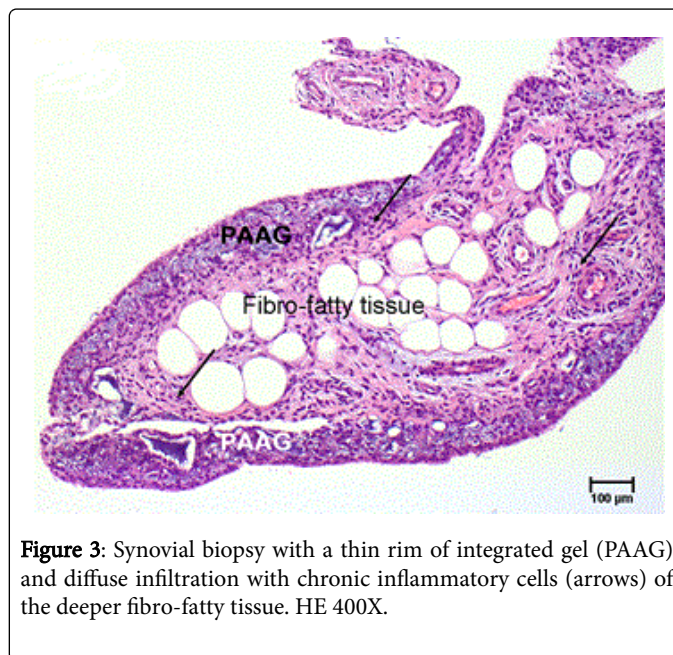


**Figure 2:** Synovial biopsy with a superficial rim of integrated polyacrylamide gel (PAAG) containing areas of fibrosis (arrows). The deeper tissue is characterized by firm fibrosis (fibrous tissue). HE 400X.

The deeper part of the synovial membrane was in some biopsies characterized by a dense fibrous tissue (Figure 2) and in others by loose fibro-fatty tissue (Figure 3). Diffuse infiltration with chronic inflammatory cells was seen in the latter (Figure 3, arrows).

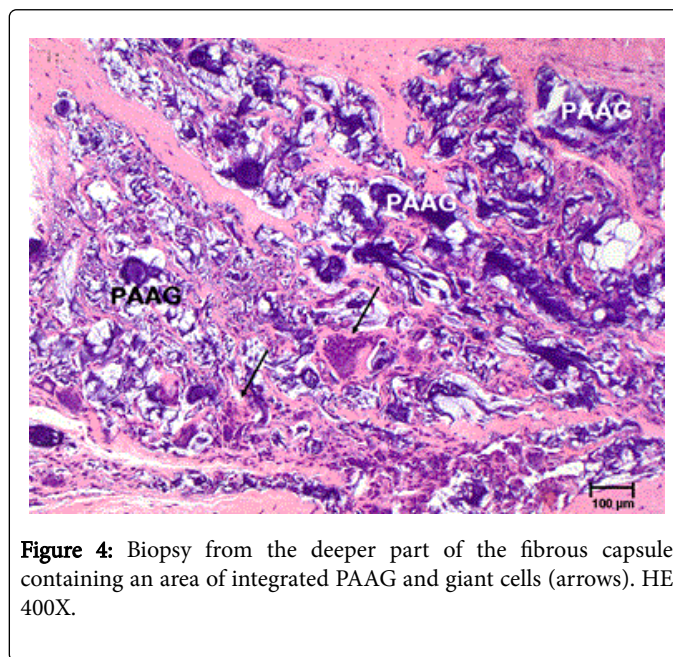
Within the integrated layer of PAAG, areas of fibrosis were seen, either as a horizontal band immediately beneath the surface cells or as fibrous strands inside the integrated gel (Figure 2, arrows).

This fibrosis was only seen in one area with dense fibrous connective tissue of the deeper parts. The surface was covered by an intact lining of normal-looking synovial cells (Figure 2). There were no areas of necrosis, calcifications or fibrinous exudate.



**Figure 3:** Synovial biopsy with a thin rim of integrated gel (PAAG) and diffuse infiltration with chronic inflammatory cells (arrows) of the deeper fibro-fatty tissue. HE 400X.

Two biopsies encompassing the deeper part of the capsule presented foci of partially integrated gel and foreign body giant cells (Figure 4, arrows) with an appearance similar to what has previously been described after injection directly into soft tissues [6].



**Figure 4:** Biopsy from the deeper part of the fibrous capsule containing an area of integrated PAAG and giant cells (arrows). HE 400X.



## Discussion

Direct injection of PAAG into soft tissues is known to elicit an initial, intense foreign body reaction followed by tissue integration, which in the pig is complete after 14 months (for a 0.1 mm<sup>3</sup> deposit) [6]. In this first histologically reported case of intra-articular injection of PAAG in the human knee, an integrated layer covered by synovial surface cells and augmenting the thickness of the synovial membrane, had already formed at 9 months (Figures 2 and 3). A similar pattern was also seen in the synovial membrane of normal rabbit knee joints and in horse joints with clinical signs of OA [8]. Histological signs of OA (synovitis and fibrosis) were in this case also found in the synovial membrane (Figures 2 and 3) and occasionally within the layer of integrated PAAG (Figure 3).

Assuming the gel enters the synovial membrane from the cavity and the synovial cells relocate on top of this gel after it has become integrated, the question arises, how did the fibrosis materialize? In PAAG augmented soft tissues it has been shown that pronounced fibrosis develops in cases with chronic inflammation [12], and chronic inflammatory cells, in particular macrophages, are well-known producers of fibrosis factors, in particular TGF- $\beta$  [13-15]. It is therefore most likely that the inflammatory cells of the synovitis were also responsible for the fibrous tissue seen within the integrated gel (Figure 2).

The presence of more deep-seated areas of gel associated with typical signs of a foreign-body inflammatory reaction was probably not an incidental observation. The synovium of the knee is known to be folded, and it may be difficult to avoid injecting intra-synovially without any other visual guidance than ultrasound.

In conclusion, these first biopsies from a pain-free human knee joint with synovitis and fibrosis, which was treated with intra-articular PAAG injections nine months previously, demonstrate a superficial synovial layer of integrated gel as well as deeper capsular deposits of integrated gel, both of which may contribute to the analgesic effect.

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