Gadolinium Deposits Could Influence the Course of Encapsulating Peritoneal Sclerosis

Encapsulating peritoneal sclerosis (EPS) is a rare but devastating complication of peritoneal dialysis (PD) (1–6). It remains unclear, why some patients develop EPS and some do not. Therefore, triggering factors, which promote the transition of simple sclerosis to EPS, are still under intensive investigation. The incidence of EPS increases with time on PD, a high peritonitis rate, younger age, smoking and glucose exposure (4, 7–9). Encapsulating peritoneal sclerosis may occur when the patient is still on PD, but frequently becomes apparent after renal transplantation or switching patients to hemodialysis (10). There are several theories about the pathogenesis of EPS. The most accepted is the two-hit model. Peritoneal dialysis treatment itself is the first hit, for instance as a consequence of low biocompatibility of the PD fluids causing damage of the peritoneal membrane. This damage occurs generally in PD patients over years and leads to simple sclerosis but not necessarily to EPS. When the second hit occurs, for example an inflammatory stimulus (e.g. bacterial peritonitis), or discontinuation of PD, EPS can develop (11).

Previous exposure to gadolinium-based contrast material during magnetic resonance imaging (MRI) has been linked to a disease called nephrogenic systemic fibrosis (NSF) (12), particularly after administration of Omniscan (Gadodiamide, GE Healthcare Buchler GmbH & Co. KG, Braunschweig, Germany) (13). Actually, there are no reports of involvement of the peritoneal membrane in patients with NSF. Recently, Goffin *et al.* reported that no trace of gadolinium was present in 4 peritoneal samples (2 EPS and 2 PD patients) (14).

In the present study, we compared peritoneal biopsies of 1 EPS patient presenting with a remarkably severe course of EPS to 4 EPS patients with an excellent outcome using immunostaining and ultrastructural analysis.

METHODS

We investigated peritoneal biopsies of 5 EPS patients who were exposed to gadolinium prior to surgery (baseline characteristics were shown in Table 1). All patients were late-stage EPS patients requiring laparotomy with peritonectomy and enterolysis due to symptoms of bowel obstruction. During this procedure, peritoneal biopsies of the visceral peritoneum were taken. The time period between gadolinium exposure and peritoneal biopsy ranged from 6 to 1,498 days.

Immunostaining against transforming growth factor β 1 (TGF- β 1), CD34 and CD68 were done following routine protocols (15). Conventional electron microscopy including elemental analysis of gadolinium, calcium and iron using the electron energy-filtered microscope operation mode and electron energy-loss spectroscopy (EELS) was performed as described previously (16).

RESULTS

We recently identified 3 different macroscopic phenotypes of EPS (which were categorized as Type I through III) (17). In this study 1 patient had Type I, 1 patient type II and 3 patients type III.

Currently, 4 out of 5 EPS patients are alive. During several follow-up time points, 3 out of 4 patients had no complaints associated with EPS and only 1 patient had rare complaints of abdominal pain throughout the day. All patients gained weight and, except 1 patient, no re-operation due to recurrent disease was performed. Years after surgery, 1 patient died due to heart failure not related to EPS. One patient had a severe course of EPS requiring reoperation due to 4 recurrent episodes. This patient had none of the previously described “triggering factors” for development of EPS. He had only 1 period of bacterial peritonitis (vs 3, 3, 5, 2 periods of peritonitis in the remaining patients) and he was on PD at time of MRI.

No systemic signs of NSF appeared in any of the patients within the follow-up period.

Histopathological analysis showed denudation of the mesothelium in all samples. In 4 out of 5 samples, slightly vascularized extensive submesothelial collagen bundles, and few blood vessels with a low number of inflammatory cells could be detected. One sample showed highly vascularized submesothelial collagen bundles, and few blood vessels with scarce inflammatory cellular infiltration.

Immunostaining revealed several hot spots of arteriolar endothelial cells expressing CD34 and several macrophages with expression of CD68 in all samples. Inflammatory cells expressing TGF- β 1 were present in all samples. There were no differences concerning the expression of all markers

TABLE 1
Baseline Characteristics of Study Patients

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at surgery (years)	38	51	22	26	60
Sex	Male	Male	Male	Male	Male
Treatment modality at gadolinium exposure	HD	HD	HD	PD	PD
MRI contrast material	Magnevist	Dotarem	Magnevist	Omniscan	Magnevist
Dose of contrast material	17 mL	15 mL	15 mL	27 mL	15 mL
Period of dialysis at exposure (months)	132	96	51	18	19
Period of exposure to biopsy (days)	6	42	23	1498	42
EPS Type (17)	III	III	II	III	I
Peritonitis episodes	3	3	5	1	2
Icodextrin	Yes	No	No	Yes	No
Diabetes	No	No	No	No	No
Hypertension	Yes	Yes	Yes	Yes	Yes
Medical therapy					
Intravenous iron infusions	Yes	Yes	Yes	Yes	Yes
ACEI	No	No	Yes	No	Yes
Calcium supplements	Yes	Yes	Yes	Yes	No
Laboratory findings					
Hb (g/dL [13–18])	11.4	10.9	8.5	11.1	8.7
Phosphate (mmol/L [0.68–1.68])	1.72	1.66	1.33	2.09	0.99
Calcium (mmol/L [1.90–2.70])	2.16	2.00	2.44	2.13	2.39
PTH (pmol/L [1.1–7.3])	10.1	21.3	12.2	0.6	38.1
Albumin (g/dL [3.5–5.0])	N.D.	3.6	3.4	2.9	1.6
CRP (mg/dL [0.1–0.5])	2.2	5.2	18.0	0.5	14.9
Histopathological analysis					
CD34+ endothelial cells	+	+	+	+	+
TGF- β 1+ inflammatory cells	+	+	+	+	+
CD68+ cells	+	+	+	+	+
Electron microscopy					
Electron dense inclusions	+	+	+	+	+
EELS spectral analyses for Gd	-	-	-	+	-

HD = hemodialysis; MRI = magnetic resonance imaging; Hb = hemoglobin; EPS = encapsulating peritoneal sclerosis; PTH = parathyroid hormone; ACEI = angiotensin converting enzyme inhibitors; N.D. = not determined; CRP = c-reactive protein; + = positive; - = negative; EELS = electron energy-loss spectroscopy; Gd = gadolinium.

between the patients. None of the markers were expressed by peritoneal fibrocytes (Figure 1).

Regarding conventional electron microscopy, electron dense inclusions were present in all peritoneal biopsies (in edematous loosened cytoplasm of few fibroblasts, intracellularly and interstitially between collagen fibers or macrophages). The EELS spectral analyses of those inclusions were negative for gadolinium in 4 out of 5 samples. In 1 patient (Patient 4) EELS spectral analysis was positive for gadolinium (Figure 2).

DISCUSSION

Just like EPS, NSF is a rare disease of unknown etiology. Nephrogenic systemic fibrosis is linked to a previous

exposure to gadolinium-based contrast material in patients with chronic kidney disease particularly after exposure to Omniscan (12,13,18). Initially, gadolinium deposits were found in the skin, but involvement of other organs has been demonstrated in various patient reports using EELS and electron spectroscopic imaging (ESI) (16,19). Gadolinium might induce a proinflammatory process leading to NSF. Typically, the affected tissues were infiltrated by CD34+, CD68+ fibroblasts, and inflammatory cells expressing TGF- β 1 (12). The macroscopic appearance and the fibrosing process of the disease, which resembles very much the sclerosing process in NSF, led to the discussion that EPS could be a localized form of NSF.

Goffin *et al.* (14) were the first group to study peritoneal biopsies from 2 EPS patients (both received

Figure 1 — Patient 4: (A) Arteriolar endothelial cells expressing CD34 (magnification 200x). (B) Macrophages expressing CD68 (magnification 200x). (C) Inflammatory cells with expression of TGF- β 1 (magnification 200x). None of the markers (CD34, CD68, TGF- β 1) were expressed by peritoneal fibrocytes as seen in nephrogenic systemic fibrosis.

Figure 2 — Patient 4: (A) Electron microscopic aspect of the deparaffinised peritoneal membrane fragment showing bundles of collagen, some profiles of cellular protrusions, and 2 very electron dense inclusions lying free in edematous interstitium (original magnification $\times 5,000$). (B) Higher magnification of the Gd deposition with the encircled spot area for the EELS-analysis (original magnification $\times 40,000$). (C) Parallel EELS spectrum displaying the recorded Gd signal (in red) of the deposit in the tissue and the superimposed reference Gd signal (in green) from the elemental atlas for comparison. Gd = gadolinium; EELS = electron energy-loss spectroscopy.

Omniscan), and 2 long-term PD patients (1 patient received Magnevist (Bayer HealthCare, Leverkusen, Germany) the other had no MRI prior to biopsy) after gadolinium exposure using ultrastructural analysis and immunohistochemistry. None of the biopsies showed gadolinium chelates in the peritoneal membrane. In our study, the patient with the poorest outcome showed gadolinium deposits in the peritoneal membrane after exposure to Omniscan.

It is well accepted that an inflammatory stimulus (e.g. bacterial peritonitis) or discontinuation of PD might act as “second-hit” in the development of EPS (11). Gadolinium chelates as “second-hit” for development of EPS have never been described. There are some special conditions regarding the clinical course of disease of the gadolinium-positive patient compared to all others. Compared to all late stage EPS patients ($n > 60$) of our

center, this particular patient underwent by far the poorest disease course (17). He underwent laparotomy with peritonectomy and enterolysis and suffered 4 relapses with 4 consecutive re-operations. It is noteworthy that Omniscan (most cases of NSF had received Omniscan [13]) was used only in this patient, whereas the others received Magnevist (gadopentetate dimeglumine) and Dotarem (Guerbet GmbH, Sulzbach, Germany) (gadoterate meglumine). Remarkably, the patient had none of the previously described “triggering factors” for development of EPS. According to the published classic risk factors for EPS, this patient would have been scaled to the lower risk group for development of EPS.

In conclusion, despite the presence of gadolinium deposits within the peritoneal membrane of 1 patient, the absence of systemic signs of NSF together with the histopathological findings argue against the hypothesis

that EPS represents a localized form of NSF. The role of gadolinium as a risk factor for severe course of the disease should be taken into account. In particular, the use of Omniscan in long-term PD patients with pre-existing peritoneal fibrosis should be avoided.

DISCLOSURES

The authors declare that they have no financial conflicts of interest. They also declare that this manuscript has not been published previously except in abstract form.

Joerg Latus¹
Eric Goffin²
Josef A. Schroeder³
Peter Fritz⁵
German Ott⁵
Christoph Ulmer⁶
Wolfgang Steurer⁶
Martin Kimmel¹
Dagmar Biegger⁴
Stephan Segerer⁷
M. Dominik Alscher¹
Niko Braun^{1*}

Department of Internal Medicine,¹

Division of Nephrology,

Robert-Bosch-Hospital, Stuttgart, Germany;

Department of Nephrology,²

Université Catholique de Louvain,

Cliniques Universitaires St Luc, Brussels, Belgium;

Department of Pathology,³

Central EM Unit,

University Medical Center, Regensburg, Germany;

Dr. Margarete-Fischer-Bosch Institute of

Clinical Pharmacology,⁴

Stuttgart, Germany;

Department of Diagnostic Medicine,⁵

Division of Pathology,

Robert-Bosch Hospital, Stuttgart, Germany;

Department of General, Visceral and Trauma Surgery,⁶

Robert-Bosch Hospital, Stuttgart, Germany;

Division of Nephrology,⁷

University Hospital, Zurich, Switzerland

* e-mail: Niko.braun@rbk.de

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doi: 10.3747/pdi.2013.00137