7T-MR imaging in a new murine model of colitis

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**Aims and objectives**

Activity assessment of inflammatory bowel diseases (IBD) in humans is currently performed with MRI [1]. Assessing inflammation with MR imaging in experimental murine models could be important for drug-screening studies. However, classical murine models of colitis obtained with DSS (dextran sulfate sodium) in drinking water or TNBS (trinitrobenzene-sulfonic acid) enema are poorly reproducible [2-4].

Bowel radiation is well known to give an acute inflammation, by killing the epithelial stem cells in a crypt, then as the epithelial cells migrate up the crypt and are eventually shed into the intestinal lumen; the crypt cannot be repopulated with epithelial cells, and consequently involutes. When this happens to a large proportion of crypts in a region of intestine, normal barrier function is lost which leads to the exposure of the normally sterile lamina propria to luminal microbes. This triggers an acute inflammatory response associated with immune cellular infiltrates [5].

So our purpose was to assess MR imaging in a new model of radiation-induced colon inflammation using pathology as reference.
Methods and materials

Colitis was induced with a localized single-dose radiation of 27 Gy (1.4Gy/min) of gamma irradiation delivered by a cobalt 60 source through a 2 x 3 cm window centered on the colorectal region in 16 Sprague-Dawley rats (150-200g), anaesthetized by isoflurane inhalation [6] (Fig.1).

![Fig.1: Anaesthetized rat in the cobalt 60 source; visualization of the irradiation window centered on the colorectal region](image)

References: Radiology, Hôpital Beaujon - Clichy/FR

Between two and four weeks after irradiation, MR imaging was performed under isoflurane anaesthesia using a 7.0-T system (Brucker, Ettlingen, Germany), with continuous monitoring of respiration. We used sagittal fat suppressed T2-weighted sequence to plan axial sequences (Fig.2); in this plane, respiratory-gated fat-suppressed T2- and T1-weighted and diffusion-weighted were realized. We used a T2-weighted RARE (rapid acquisition with relaxation enhancement) sequence (TR 5000 ms, TE 56 ms, matrix 192, slice 1 mm, NEX 1, field of view (FOV) 6 cm); a T1w FLASH (fast low angle shot) sequence (TR 510 ms, TE 3,8 ms, matrix 192, slice 1 mm, NEX 2, flip angle 40°, FOV 6 cm); and a diffusion- weighted sequence (spin-echo with EPI readout; TR 1250 ms, effective TR 2000-2500 ms depending on respiratory rate; TE 31 ms; NEX 1; FOV 6 cm; matrix 128; slice 1 mm; b values 0, 50, 150, 300, 500 and 700 s/mm²).

Same MR imaging was performed in ten, age-matched normal rats which were used as controls.
Fig. 2: Sagittal fat suppressed T2-weighted sequence centered on the colorectum of a control rat (a) and an irradiated rat (b)

References: Radiology, Hôpital Beaujon - Clichy/FR

MR criteria were wall thickness (mm), wall signal intensity on T2- and T1-weighted images and apparent diffusion coefficient (ADC, \( \times 10^{-3} \) mm\(^2\)/s).

For all measurements, rectal wall was delineated by a manually drawn region of interest (ROI) (at least half the circumference was included in the ROI).

Area of the ROI, mean intensity, standard deviation, minimum and maximum intensity were given by an histogram (Fig.3).

For T2- and T1-weighted sequences, rectal wall signal intensity was normalized to the paraspinous muscle signal intensity measured by another ROI in the same image.
**Fig. 3**: Axial fat suppressed T2-weighted images of a control rat (a) and an irradiated rat (b). Rectal wall is delineated by a manually drawn ROI. Area of the ROI, mean intensity, standard deviation, minimum and maximum intensity are given by an histogram. Paraspinous muscle density is measured by another ROI in the same image.

**References**: Radiology, Hôpital Beaujon - Clichy/FR

The rats were euthanized immediately after MRI by intraperitoneal injection of thiopentone. The distal colon and rectum were removed and fixed in formaldehyde. Small rings of bowel that were 0.3 cm thick were kept from the middle of the irradiated area and embedded in paraffin. Five-micrometer-thick sections were obtained at every 1000 µm and stained with hematoxylin-eosin-saffron. Histological analysis of the colon was performed by a gastrointestinal pathologist (DCH), with evaluation of neutrophil infiltration of bowel wall and mucosal ulcerations.
Images for this section:

**Fig. 1:** Anaesthetized rat in the cobalt 60 source; visualization of the irradiation window centered on the colorectal region

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**Fig. 2:** Sagittal fat suppressed T2-weighted sequence centered on the colorectum of a control rat (a) and an irradiated rat (b)

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Fig. 3: axial fat suppressed T2-weighted images of a control rat (a) and an irradiated rat (b). Rectal wall is delineated by a manually drawn ROI. Area of the ROI, mean intensity, standard deviation, minimum and maximum intensity are given by an histogram. Paraspinous muscle density is measured by another ROI in the same image.

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Results

1-Pathology

Histological evaluation showed important thickness of the mucosa with marked neutrophil infiltration in all irradiated rats except one, with important mucosal ulcerations (Fig.4).

Fig. 4: Fig.4: rectum specimen (a); Section of rectum stained with hematoxylin-eosin-saffron from a normal rat (b); Section of rectum stained with hematoxylin-eosin-saffron from an irradiated rat, with important thickness of the mucosa with marked neutrophil infiltration and mucosal ulcerations (c)

References: Radiology, Hôpital Beaujon - Clichy/Fr

2- MR imaging

a- T2-weighted sequences

Maximal rectal wall thickness measured on axial T2-weighted images was significantly different (p<0.0001) between control group (0.8±0.1 mm) and inflammation group (2.1±0.1 mm) (Fig.5 and Fig.6).
Rectal wall intensity normalized to muscle intensity measured on axial T2-weighted images was significantly different (P<0.0001) between control group (2±0.1) and inflammation group (4±0.2) (Fig.7)

**Fig. 5**: Fig.5: Axial fat suppressed T2-weighted images in control group (a) and in inflammation group (b)

*References*: Radiology, Hôpital Beaujon - Clichy/FR
Fig. 6: Maximal rectal wall thickness is significantly different ($p<0.0001$) between control group (a) (0.8±0.1 mm) and inflammation group (b) (2.1±0.1 mm)

References: Radiology, Hôpital Beaujon - Clichy/FR
Rectal wall intensity normalized to muscle intensity on axial T2-weighted images is significantly different (P<0.0001) between control group (2±0.1) and inflammation group (4±0.2).

References: Radiology, Hôpital Beaujon - Clichy/FR

**b- T1-weighted sequences**

Rectal wall intensity normalized to muscle intensity measured on axial T1-weighted images was significantly different (P<0.0001) between control group (1.1±0.1) and inflammation group (1.4±0.02) (Fig.8 and Fig.9).
Fig. 8: Axial fat suppressed T1-weighted image in control group (a) and in inflammation group (b)

References: Radiology, Hôpital Beaujon - Clichy/FR
**Fig. 9:** Rectal wall intensity normalized to muscle intensity on axial T1-weighted images is significantly different ($P<0.0001$) between control group ($1.1\pm0.1$) and inflammation group ($1.4\pm0.02$)

**References:** Radiology, Hôpital Beaujon - Clichy/FR

**c- Diffusion-weighted sequences**

Rectal wall apparent coefficient of diffusion was significantly different ($P=0.0001$) between control group ($1.51\times10^{-3} \pm 0.07 \text{ mm}^2/\text{s}$) and inflammation group ($2.06\times10^{-3} \pm 0.08 \text{ mm}^2/\text{s}$) ([**Fig. 10**](#) and [**Fig. 11**](#)).
Fig. 10: Diffusion-weighted image of signal intensity (a) and ADC map (b)

References: Radiology, Hôpital Beaujon - Clichy/FR
Fig. 11: Rectal wall apparent coefficient of diffusion is significantly different ($P=0.0001$) between control group ($1.51 \times 10^{-3} \pm 0.07$ mm$^2$/s) and inflammation group ($2.06 \times 10^{-3} \pm 0.08$ mm$^2$/s)

References: Radiology, Hôpital Beaujon - Clichy/FR
Images for this section:

**Fig. 4:** Fig. 4: rectum specimen (a); Section of rectum stained with hematoxylin-eosin-saffron from a normal rat (b); Section of rectum stained with hematoxylin-eosin-saffron from an irradiated rat, with important thickness of the mucosa with marked neutrophil infiltration and mucosal ulcerations (c)

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**Fig. 5:** Fig. 5: Axial fat suppressed T2-weighted images in control group (a) and in inflammation group (b)
**Fig. 6:** Maximal rectal wall thickness is significantly different (p<0.0001) between control group (a) (0.8±0.1 mm) and inflammation group (b) (2.1±0.1 mm)
Fig. 7: Rectal wall intensity normalized to muscle intensity on axial T2-weighted images is significantly different (P<0.0001) between control group (2±0.1) and inflammation group (4±0.2)

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Fig. 8: Axial fat suppressed T1-weighted image in control group (a) and in inflammation group (b)

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Fig. 9: Rectal wall intensity normalized to muscle intensity on axial T1-weighted images is significantly different (P<0.0001) between control group (1.1±0.1) and inflammation group (1.4±0.02)

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Fig. 10: Diffusion-weighted image of signal intensity (a) and ADC map (b)

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Fig. 11: Rectal wall apparent coefficient of diffusion is significantly different ($P=0.0001$) between control group ($1.51\times10^{-3} \pm 0.07 \text{ mm}^2/\text{s}$) and inflammation group ($2.06\times10^{-3} \pm 0.08 \text{ mm}^2/\text{s}$)

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Conclusion

Murine radiation-induced colitis is a highly reproducible model with homogeneous pathological features of a strong mucosal inflammation.

Changes related to this inflammation are reproducibly observed at high-field MR imaging; criteria which are well-correlated with inflammation are increased wall thickness, high wall signal intensity on T2- and T1-weighted images normalized to paraspinous muscle and increased apparent diffusion coefficient (ADC).
References


