GE Healthcare

Case studies with Lawrence N. Tanenbaum, MD FACR using macrocyclic CLARISCAN™ (gadoterate meglumine) injection for intravenous use

Lawrence N. Tanenbaum, MD FACR is Vice President/Chief Technology Officer Director of CT, MR, and Advanced Imaging for RadNet with over 37 years experience in the medical field. He is a member of editorial boards of several journals/educational organizations and reviewer for scientific journals. He has authored more than 100 scholarly and peer-reviewed articles, chairs educational/academic meetings, and has delivered over 2000 invited global lectures.*

PRODUCT INDICATIONS AND USE:
CLARISCAN™ (gadoterate meglumine) is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine, and associated tissues in adult and pediatric patients to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

Additional pediatric use information is approved for Guerbet LLC's Dotarem (gadoterate meglumine injection). However, due to Guerbet LLC's marketing exclusivity, this drug product is not labeled with that pediatric information.

IMPORTANT SAFETY INFORMATION ABOUT CLARISCAN™
Contraindications
History of clinically important hypersensitivity reactions to Clariscan

Please see the Boxed Warning to the right and additional Important Safety Information on the following pages. Click here for full Prescribing Information, including patient Medication Guide.

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
See full Prescribing Information for complete Boxed Warning.
Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle, and internal organs.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR <30 mL/min/1.73 m^2), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **For patients at highest risk for NSF, do not exceed the recommended Clariscan dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.**

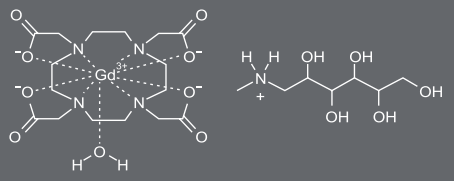
Clariscan™
(gadoterate meglumine)
injection for intravenous use

Macrocyclic, ionic GBCA

Cagelike structure encloses the Gd^{3+} ion[1]

Highest chelate stability among GBCAs[2]

Strong chemical bond[3]



Gadoterate meglumine

Case Study 1

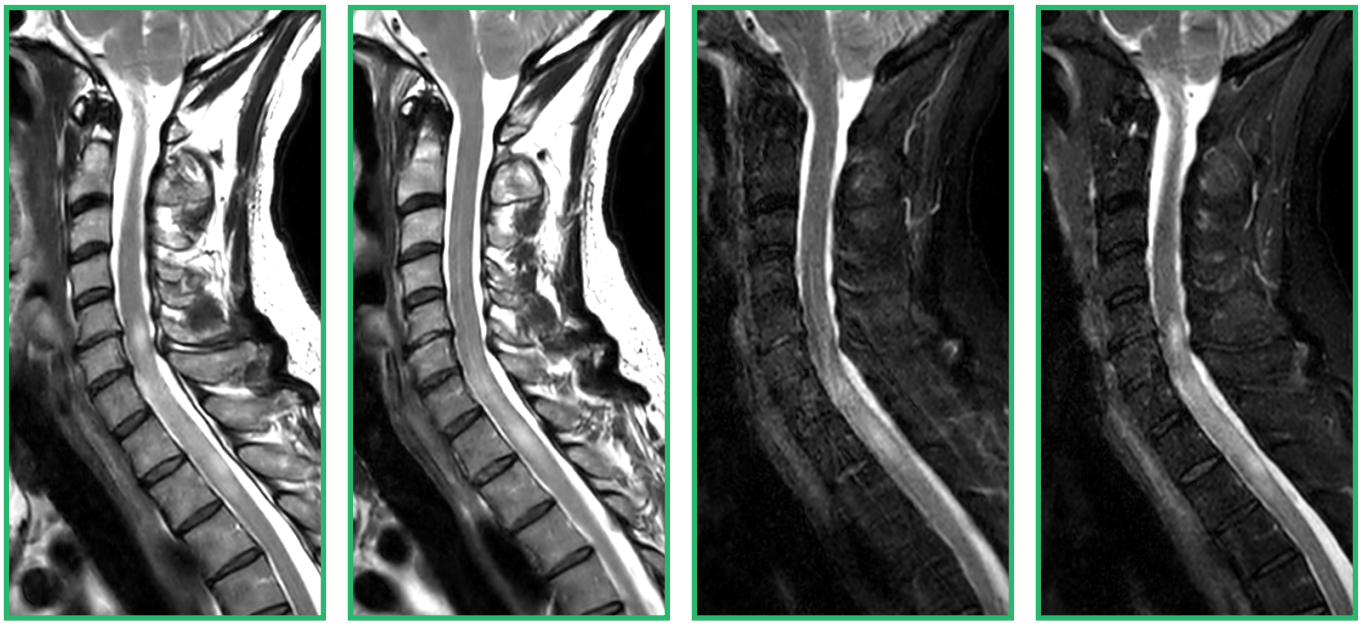
Clinical Presentation

55-year-old male weighing 160 lbs, presented with bilateral sensory and motor symptoms.
Prior brain and optic nerve imaging normal

Imaging

MRI of the cervical spine and brain with and without 16 mL of Clariscan™ (gadoterate meglumine)

T2 STIR



- **Poorly defined intramedullary lesion extending from C5-T3.**

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IMPORTANT SAFETY INFORMATION ABOUT CLARISCAN™

Warnings and precautions

- Nephrogenic Systemic Fibrosis has occurred in patients with impaired elimination of GBCAs. Higher than recommended dosing or repeat dosing appear to increase the risk.
- Hypersensitivity: Anaphylactoid/anaphylactic reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred. Monitor patients closely for need of emergency cardiorespiratory support.
- Gadolinium is retained for months or years in brain, bone, and other organs.

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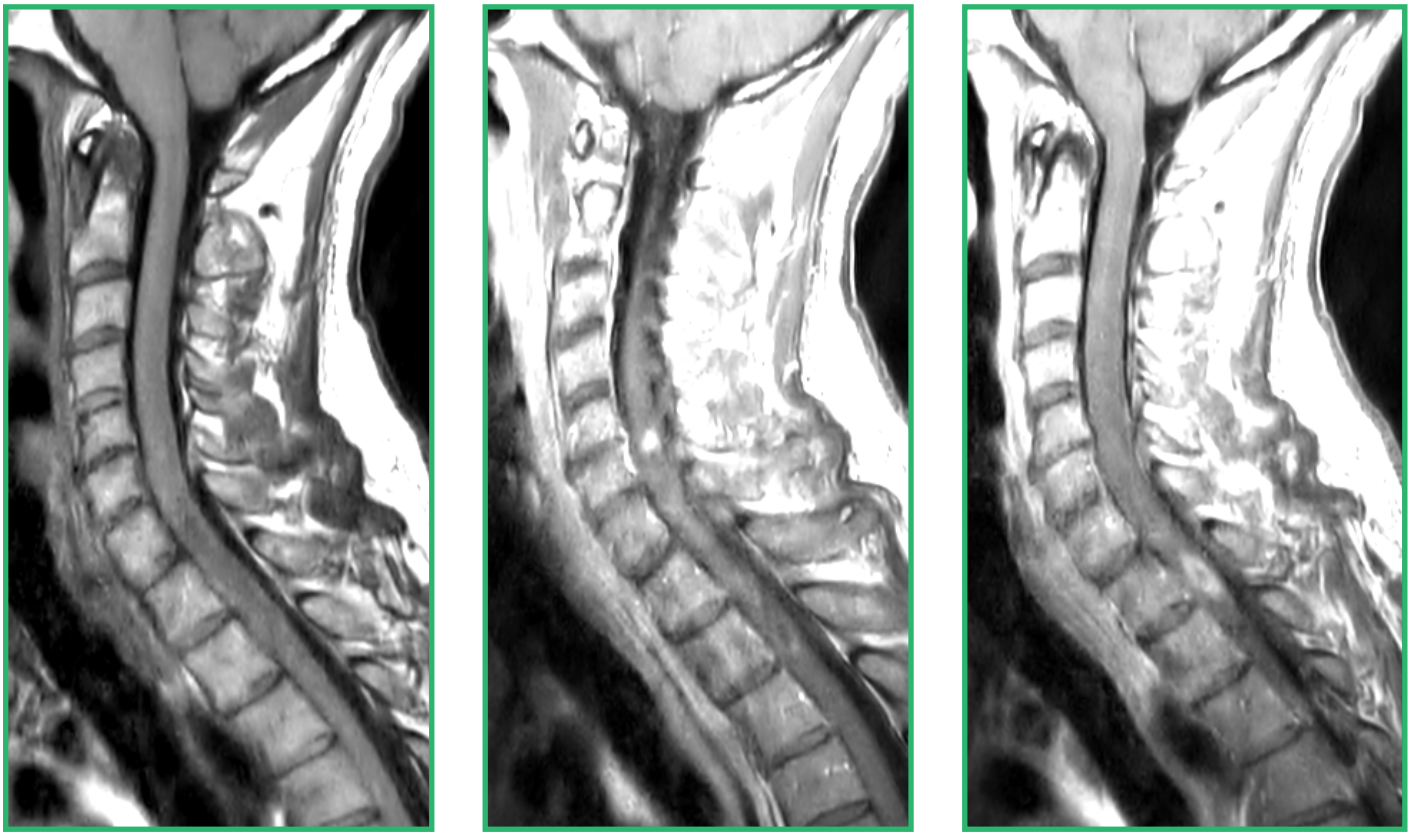
Clariscan™
(gadoterate meglumine)
injection for intravenous use

Case Study 1 (cont'd)

Precontrast T1WI — Postcontrast T1WI



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IMPORTANT SAFETY INFORMATION ABOUT CLARISCAN™ (Cont'd)

Warnings and precautions (cont'd)

- **Acute kidney injury**: In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging.

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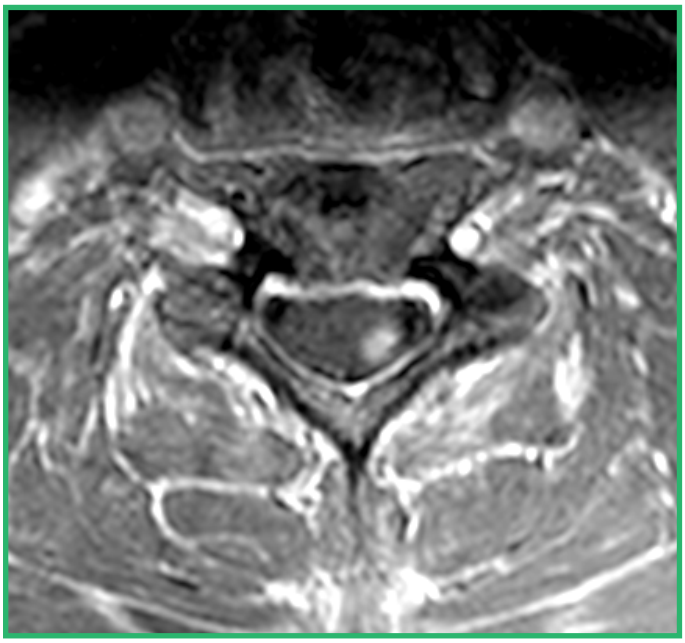
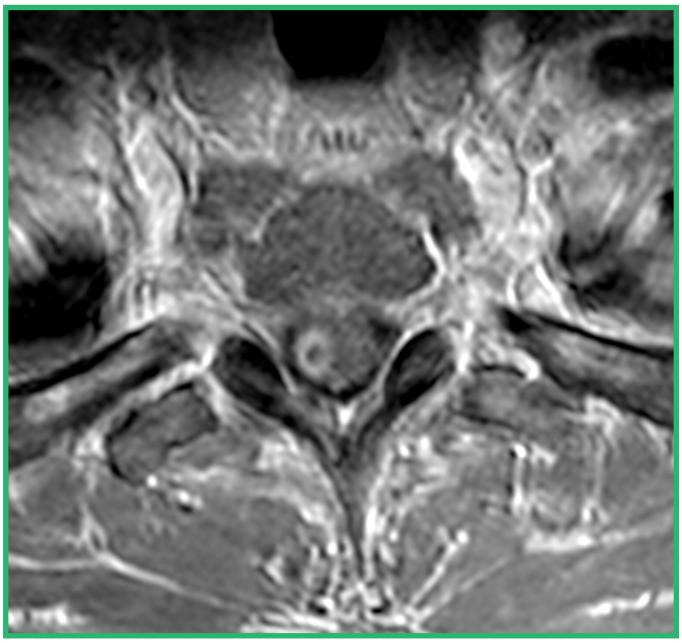
Clariscan™
(gadoterate meglumine)
injection for intravenous use

Case Study 1 (cont'd)

Postcontrast T1





- **Nodular and ring enhancing lesions within the cord consistent with myelitis**

Imaging Findings

Nodular and ring enhancing lesions within the cord consistent with myelitis.
No evidence of abnormality on brain or optic nerve imaging.

Diagnosis

MRI results are consistent with myelitis

Treatment

Medical therapy

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Clariscan™
(gadoterate meglumine)
injection for intravenous use

Case Study 2

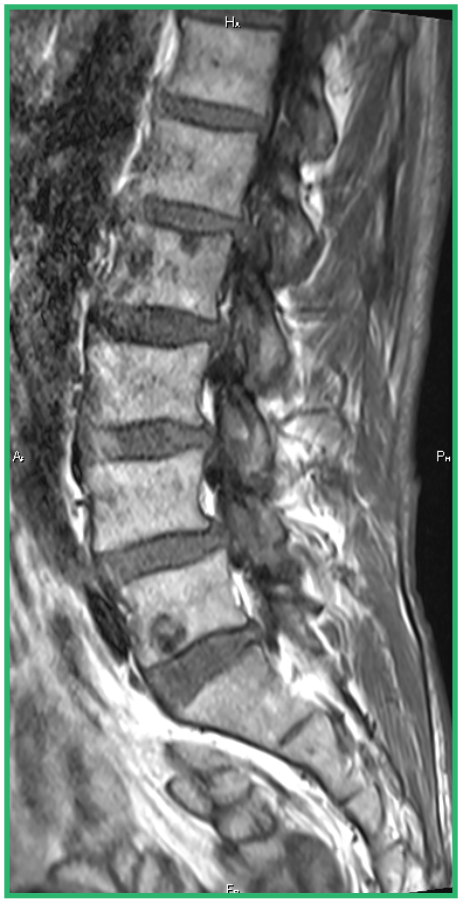
Clinical Presentation

72-year-old male weighing 140 lbs, presented with back pain; history of prostate CA

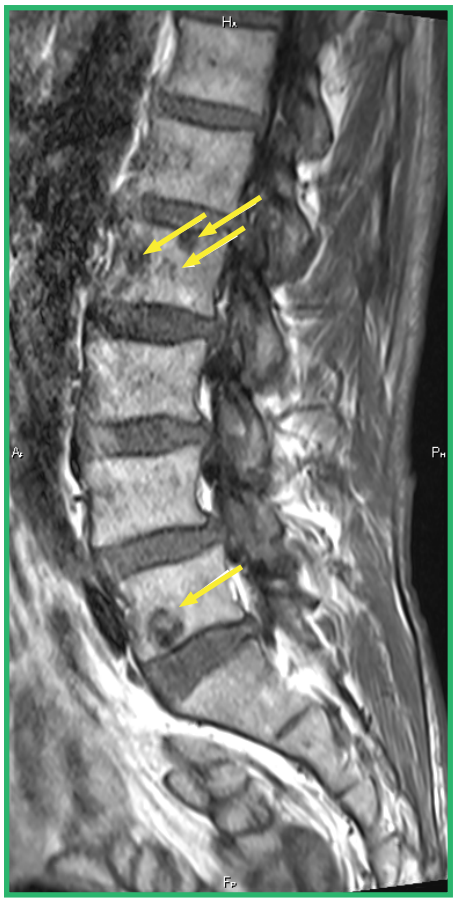
Imaging

MRI of the spine with and without 14 mL of Clariscan™ (gadoterate meglumine)

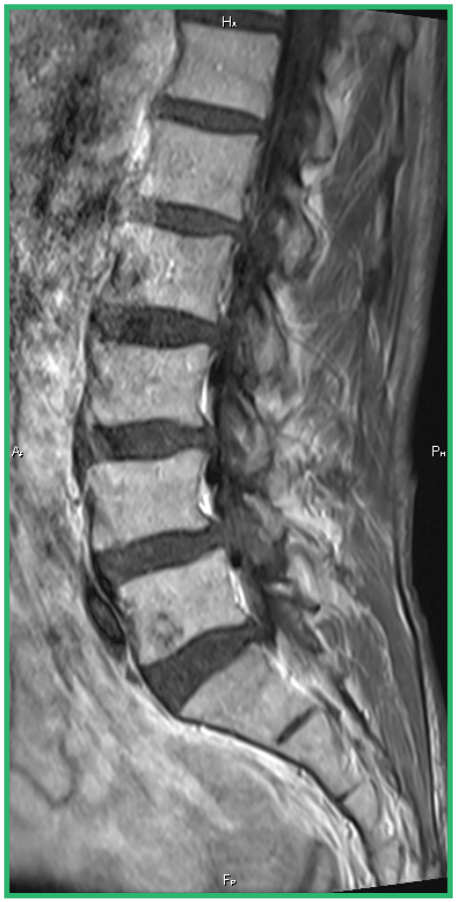
Precontrast T1



Precontrast T1



Postcontrast T1



- **Lesions at L2 and L5 which fill in/enhance postcontrast (arrows)**

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IMPORTANT SAFETY INFORMATION ABOUT CLARISCAN™ (Cont'd)

Adverse reactions

- **Extravasation and injection site reactions:** Ensure catheter and venous patency before the injection of Clariscan. Extravasation into tissues during Clariscan administration may result in tissue irritation.
- The most common adverse reactions (≥ 0.2%) associated with gadoterate meglumine in clinical trials were nausea, headache, injection site pain, injection site coldness and rash.
- Serious adverse reactions in the postmarketing experience have been reported with gadoterate meglumine. These serious adverse reactions include but are not limited to: arrhythmia, cardiac arrest, respiratory arrest, pharyngeal edema, laryngospasm, bronchospasm, coma and convulsion.

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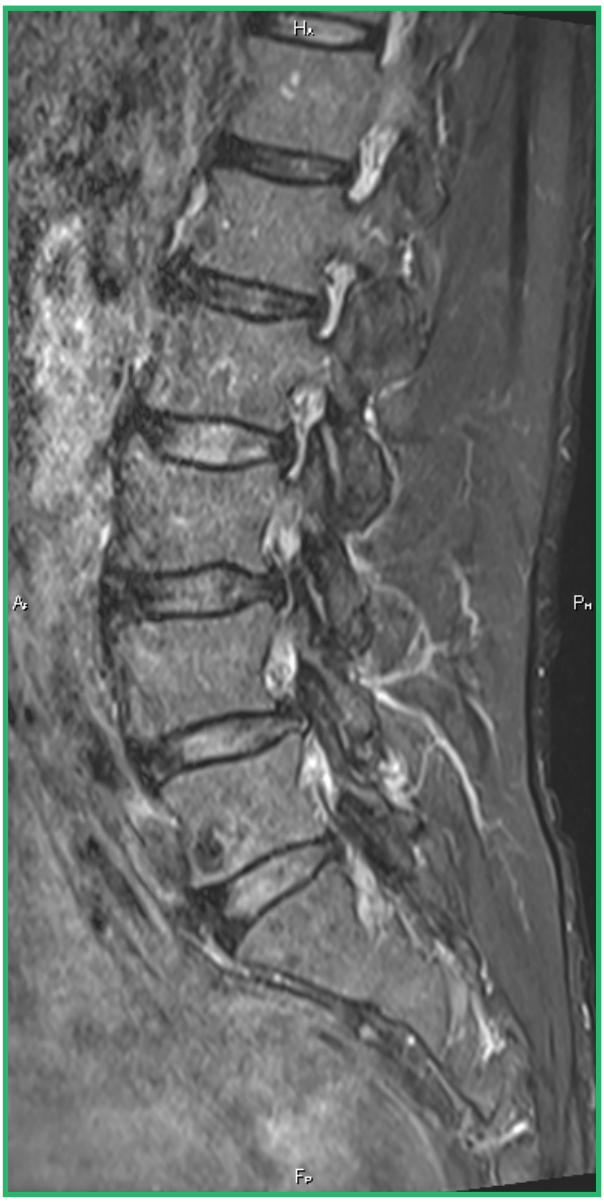
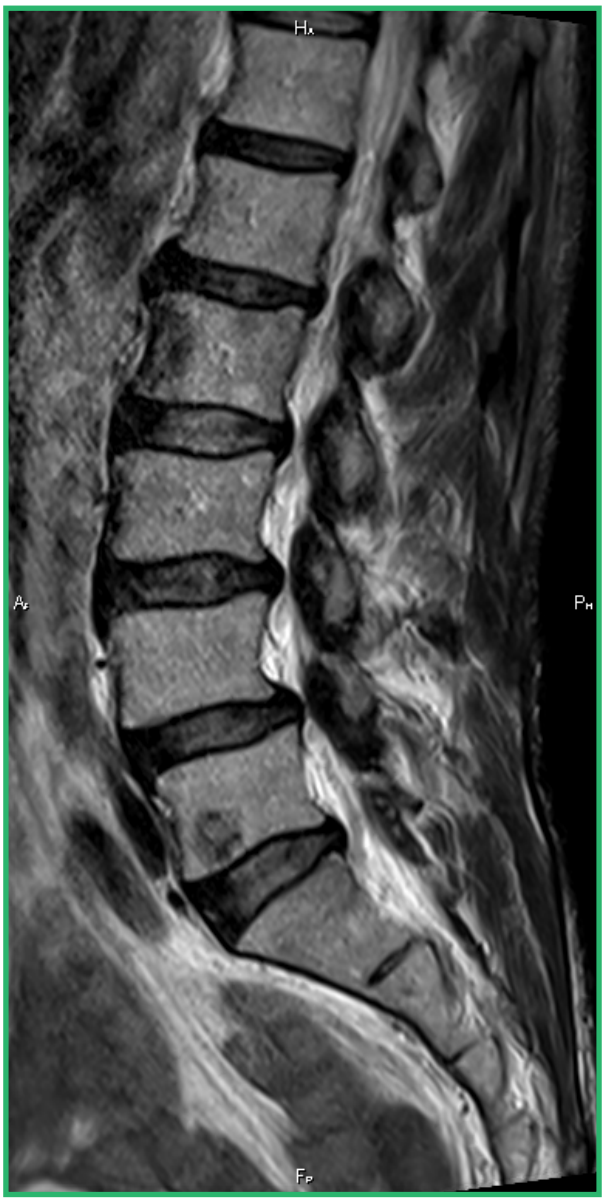
Clariscan™
(gadoterate meglumine)
injection for intravenous use

Case Study 2 (cont'd)

STIR



T2



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IMPORTANT SAFETY INFORMATION ABOUT CLARISCAN™ (Cont'd)

Use in specific populations

- **Pregnancy:** GBCAs cross the human placenta and result in fetal exposure and gadolinium retention. The human data on the association between GBCAs and adverse fetal outcomes are limited and inconclusive. Because of the potential risks of gadolinium to the fetus, use Clariscan only if imaging is essential during pregnancy and cannot be delayed. Advise pregnant women of the potential risk of fetal exposure to GBCAs.
- **Lactation:** There are no data on the presence of gadoterate in human milk, the effects on the breastfed infant, or the effects on milk production. However, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk.

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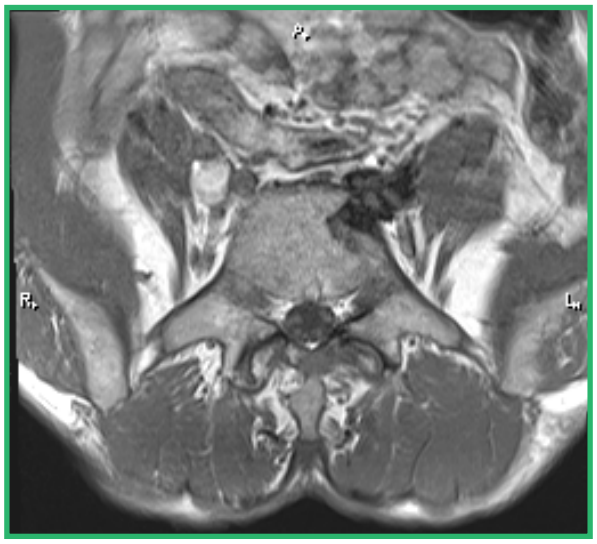
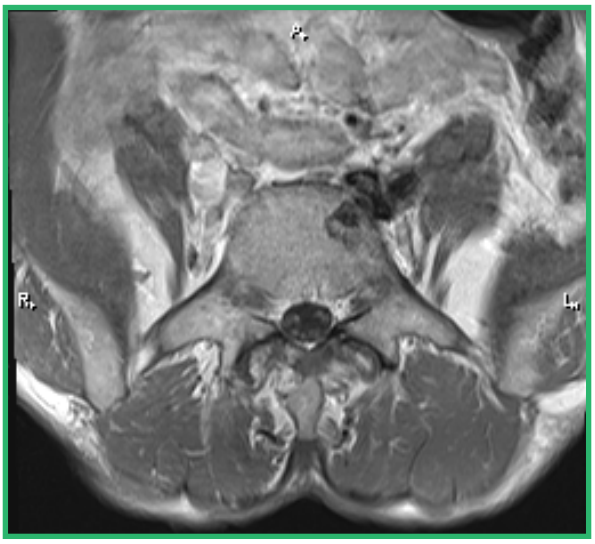
Clariscan™
(gadoterate meglumine)
injection for intravenous use

Case Study 2 (cont'd)

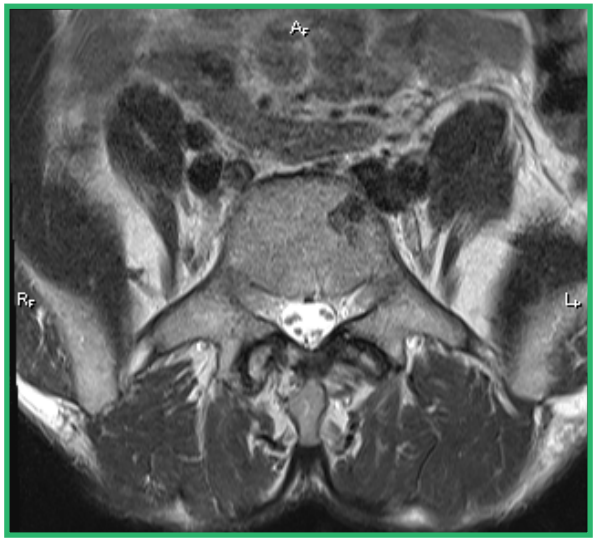
Precontrast T1



Postcontrast T1



T2



- **Partially enhancing lesion within the anterior aspect of the S1 vertebral body**

Imaging Findings

Lesions at L2 and L5 which fill in/enhance postcontrast

Diagnosis

MRI results are consistent with metastatic disease

Treatment Plan

Radiation and chemotherapy

Case Study 3

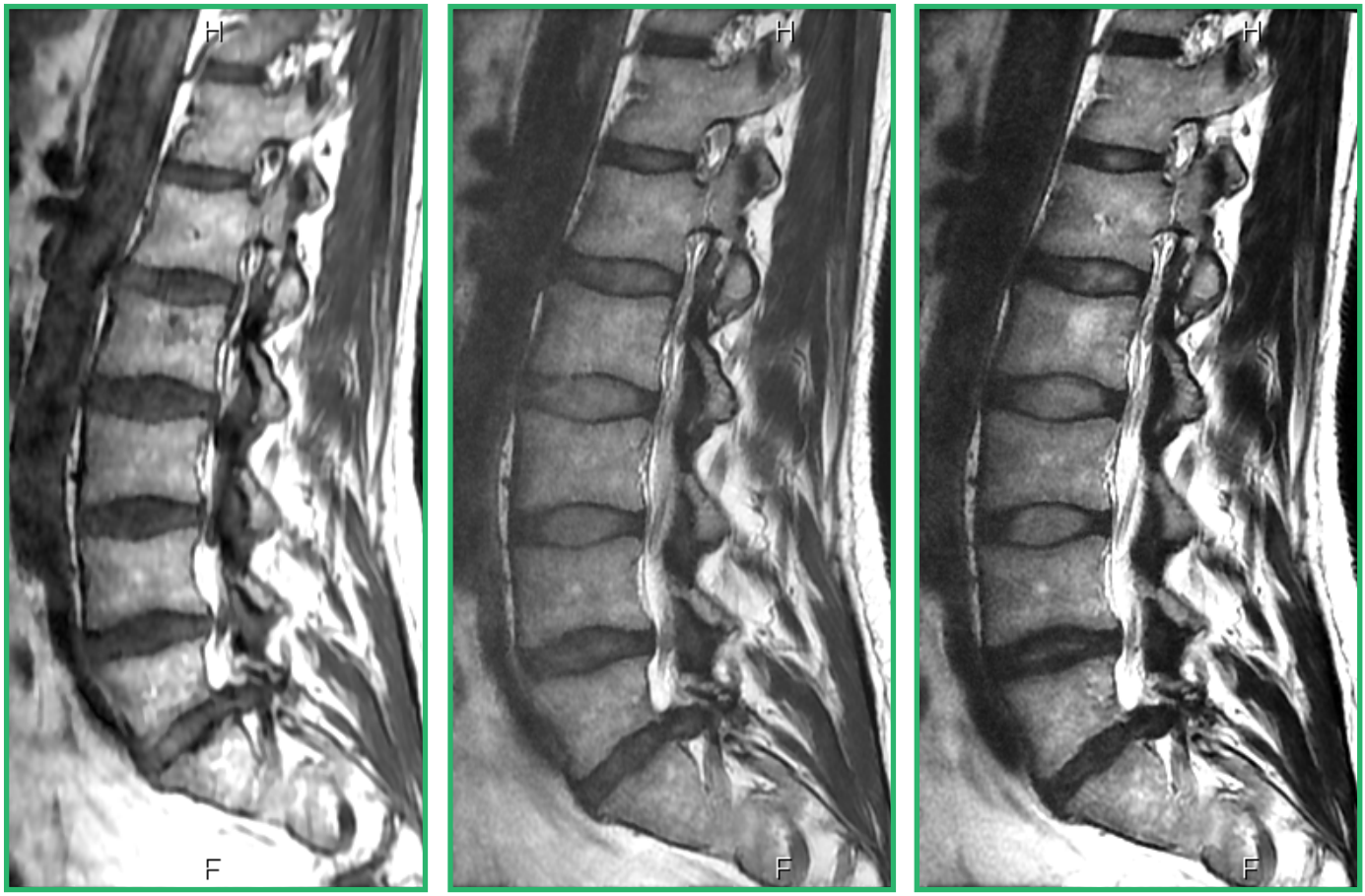
Clinical Presentation

45-year-old male weighing 190 lbs, presented with back pain and left side S1 radiculopathy; prior surgery at L5-S1

Imaging

MRI of the spine with and without 19 mL of Clariscan™ (gadoterate meglumine)

Precontrast T1 | **PD** | **T2**



- **Scans reveal abnormal anterior extradural soft tissue to the left of midline at L5-S1**

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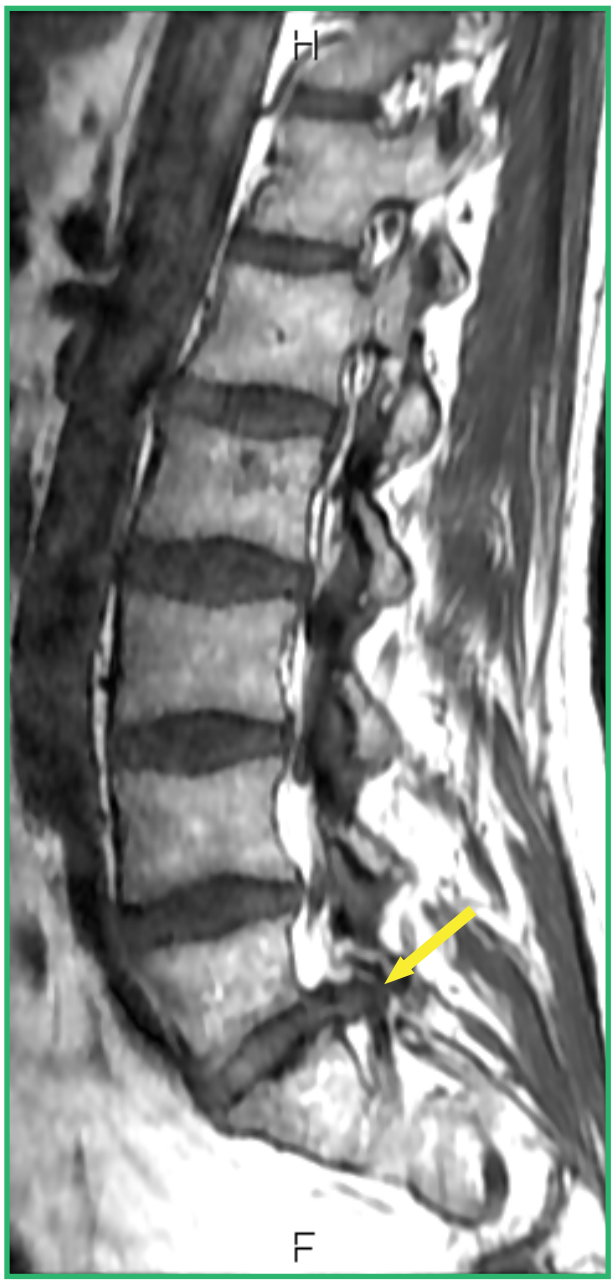
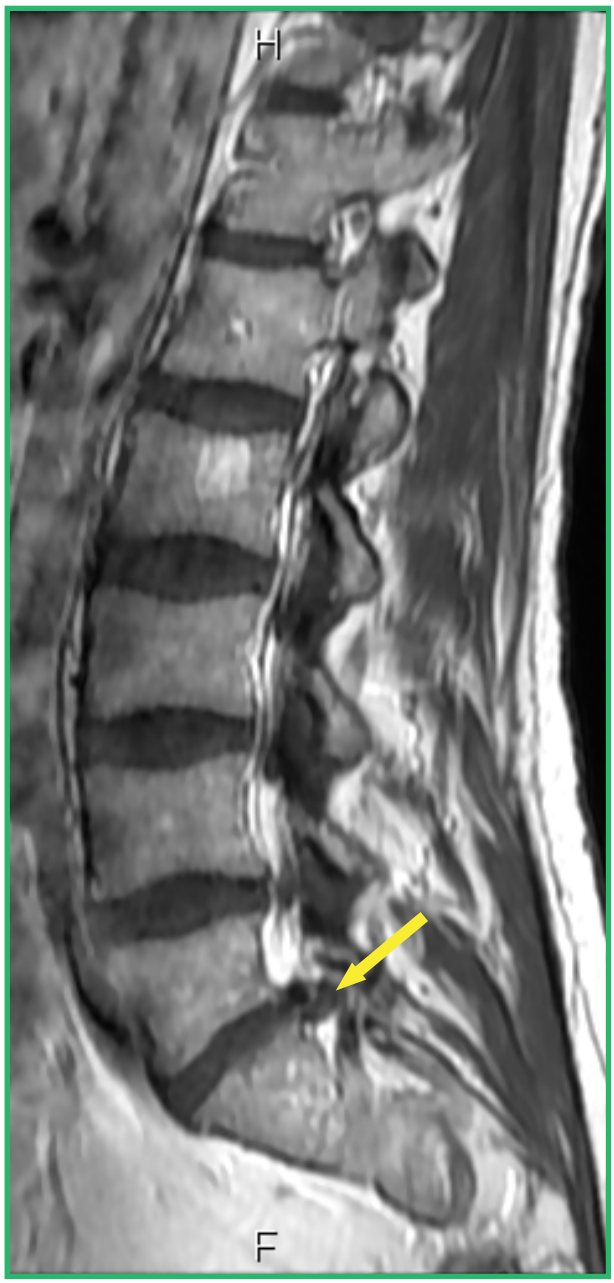
Case Study 3 (cont'd)

Precontrast T1



Postcontrast T1



- Images demonstrate anterior extradural nonenhancing tissue at L5-S1 consistent with a recurrent herniation

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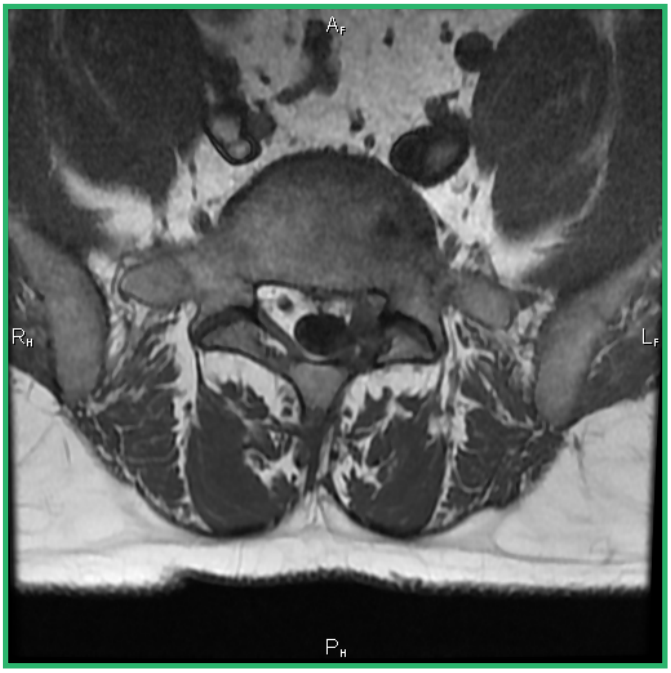
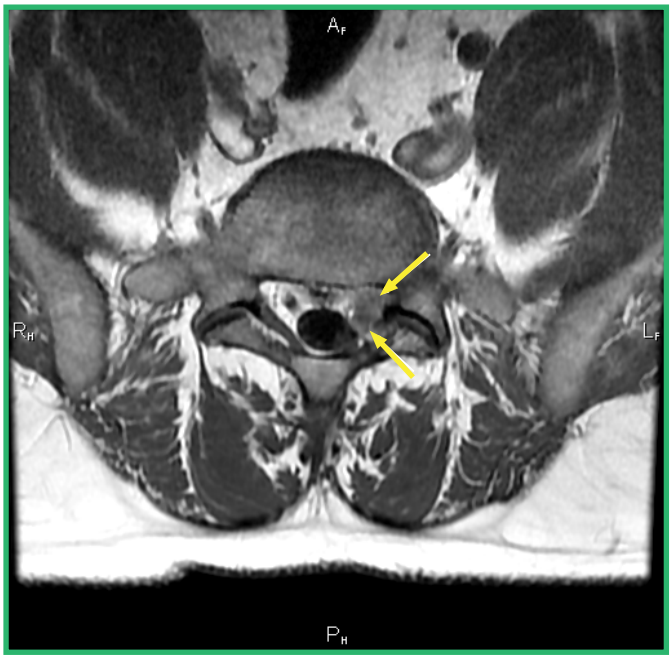
Case Study 3 (cont'd)



Precontrast T1

- **Abnormal soft tissue obscuring the tissue planes with the left S1 nerve root**



Precontrast T1

- **Island of nonenhancing tissue within a 'sea' of enhancement at L5-S1 consistent with a recurrent herniation which displaces the left S1 root posteriorly**
- **Herniated material (upper/anterior arrow)**
- **Displaced S1 root (lower/posterior arrow)**

Imaging Findings

Island of nonenhancing tissue within a 'sea' of enhancement at L5-S1 consistent with a recurrent herniation

Diagnosis

MRI results are consistent with recurrent herniation

Treatment Plan

Repeat surgery

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Clariscan™
(gadoterate meglumine)
injection for intravenous use

Case Study 4

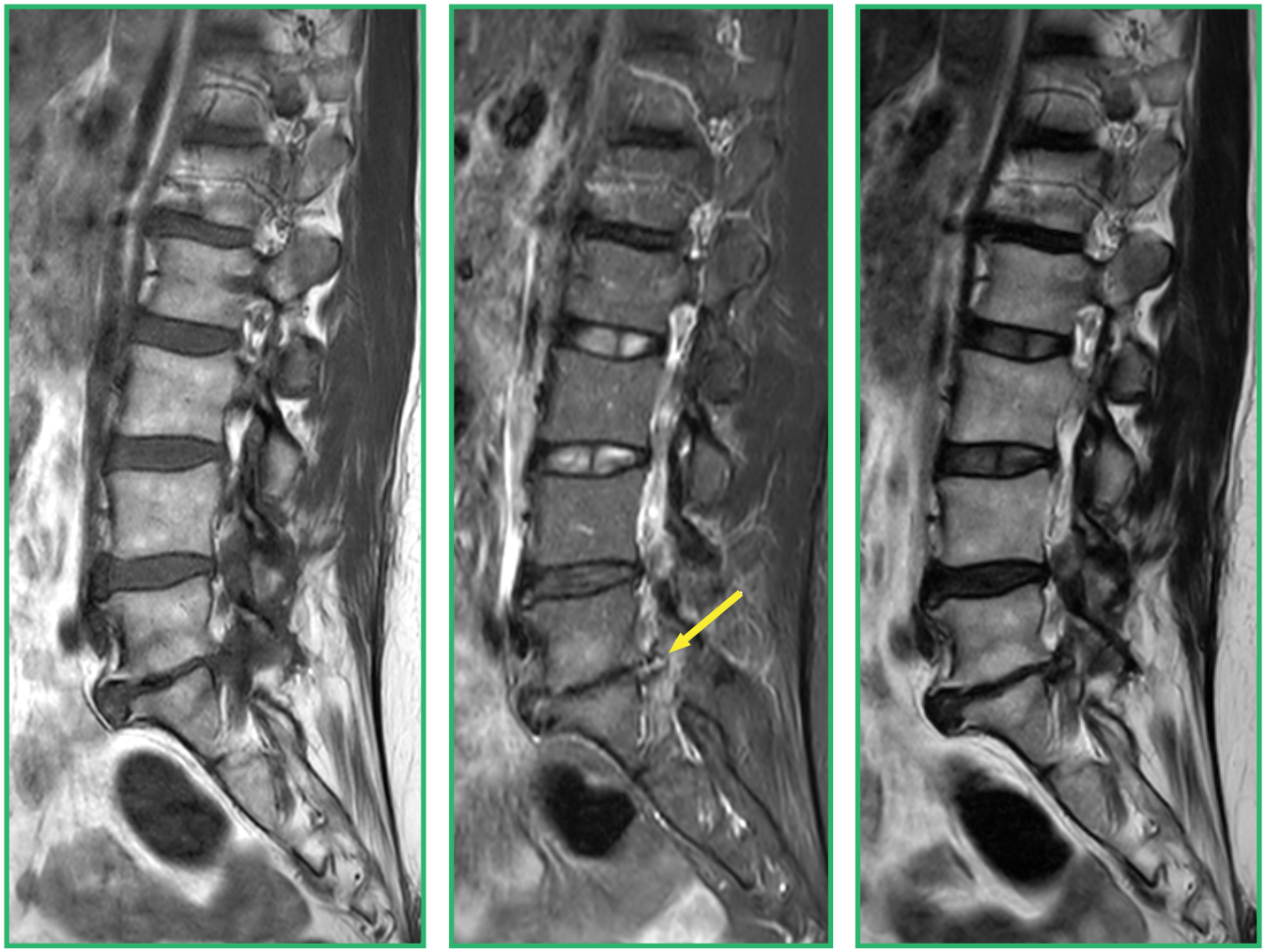
Clinical Presentation

60-year-old female weighing 140 lbs, presented with right sided back pain and right sided radiculopathy; prior surgery at L5-S1 for herniation

Imaging

MRI of the spine with and without 14 mL of Clariscan™ (gadoterate meglumine)

Precontrast T1 | STIR | T2



- **Abnormal anterior extradural tissue at the L5-S1 level which could reflect postsurgical change or recurrent herniation**

(Continued)

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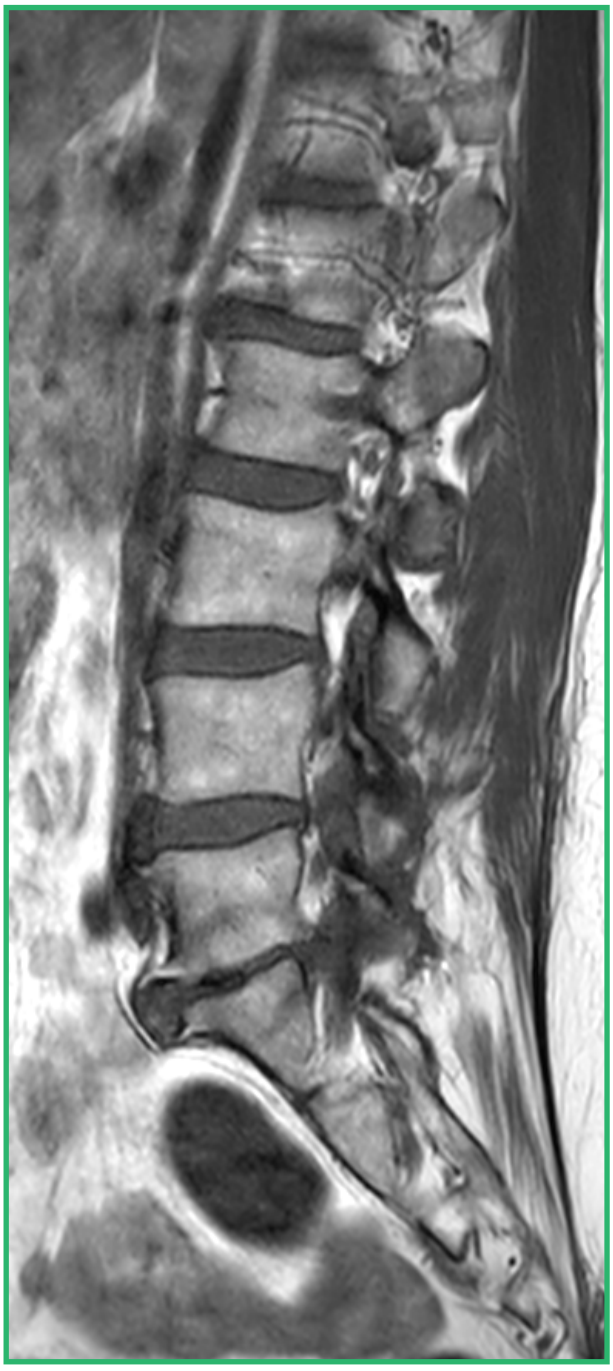
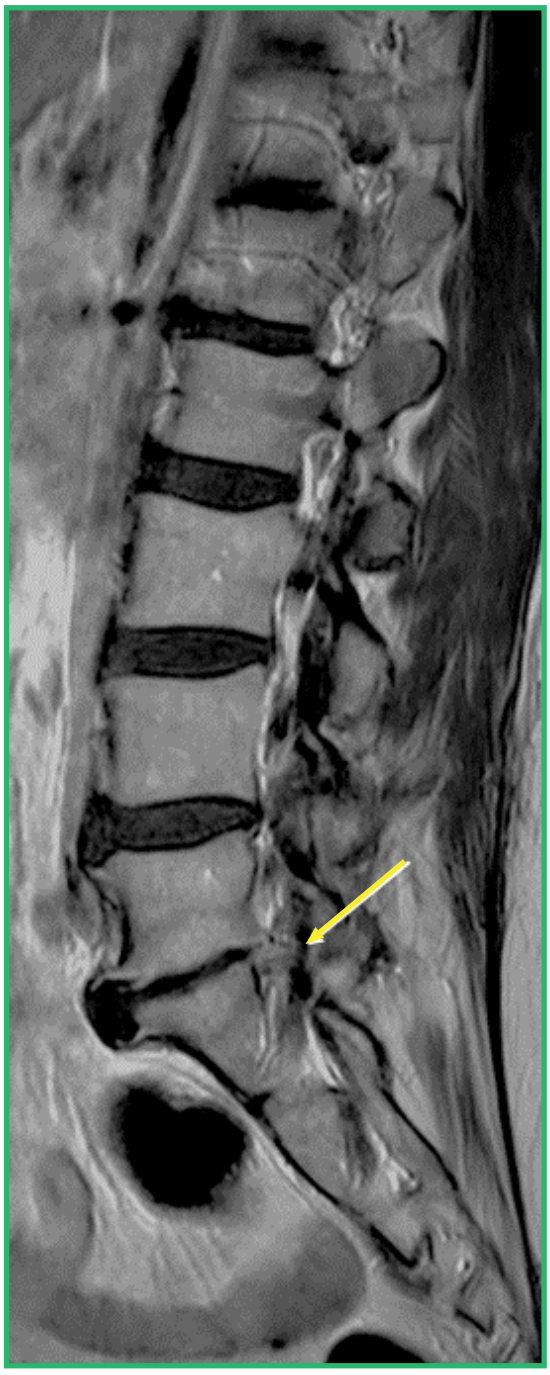
Clariscan™
(gadoterate meglumine)
injection for intravenous use

Case Study 4 (cont'd)

Precontrast T1



Postcontrast T1

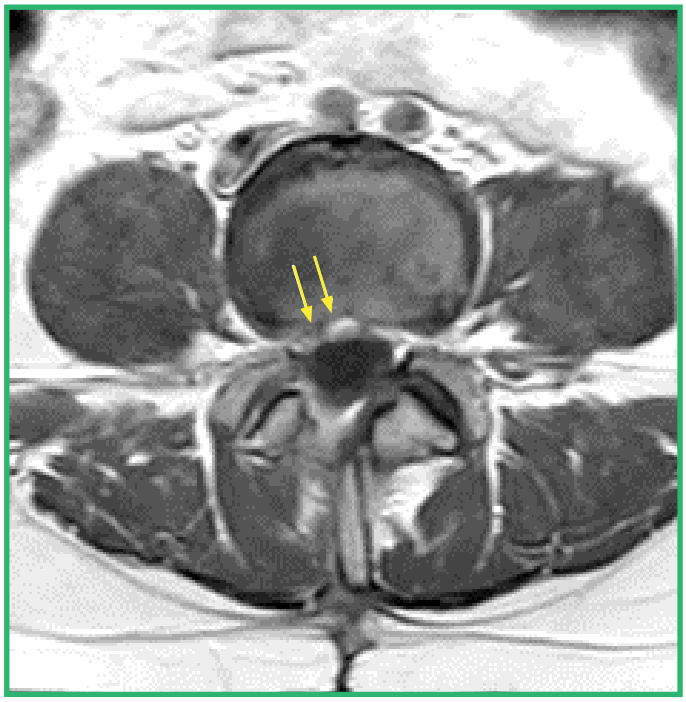


- Enhancing anterior extradural tissue at the L5-S1 level consistent with postsurgical change

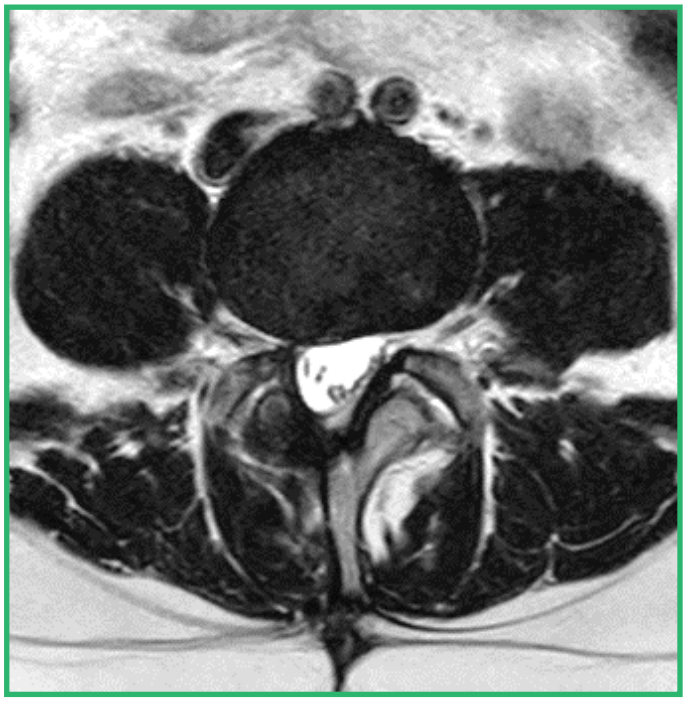
(Continued)

Case Study 4 (cont'd)

Postcontrast T1



T2



- **Right sided hemilaminotomy and enhancing epidural soft tissue consistent with treatment-related change**

Imaging Findings

Right sided hemilaminotomy and enhancing epidural soft tissue consistent with treatment-related change

Diagnosis

MRI results are consistent with postsurgical change

Treatment Plan

Conservative treatment

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Clariscan™
(gadoterate meglumine)
injection for intravenous use

Case Study 5

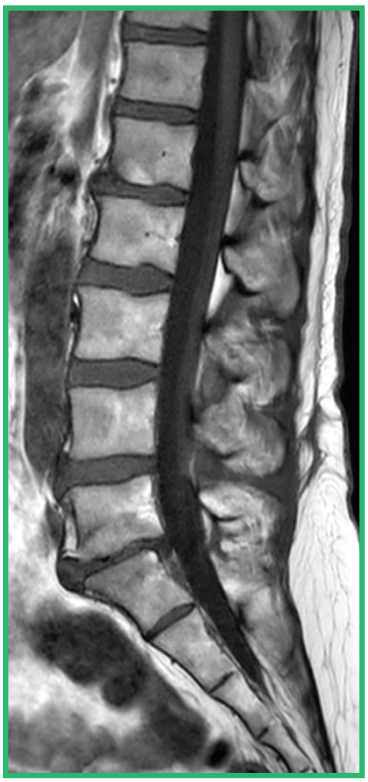
Clinical Presentation

60-year-old female weighing 140 lbs, presented with right sided back pain and right sided radiculopathy; prior surgery at L5-S1 for herniation

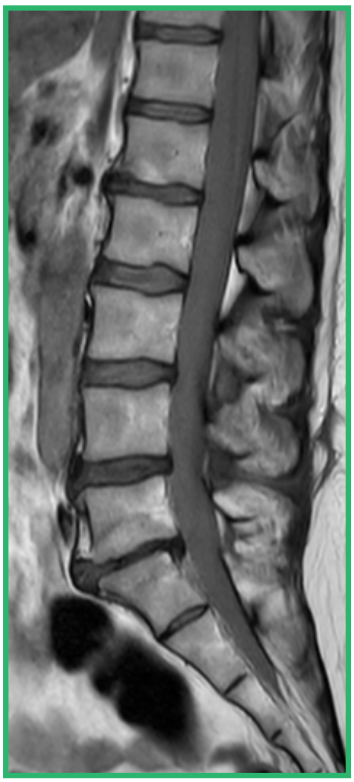
Imaging

MRI of the spine with and without 14 mL of Clariscan™ (gadoterate meglumine)

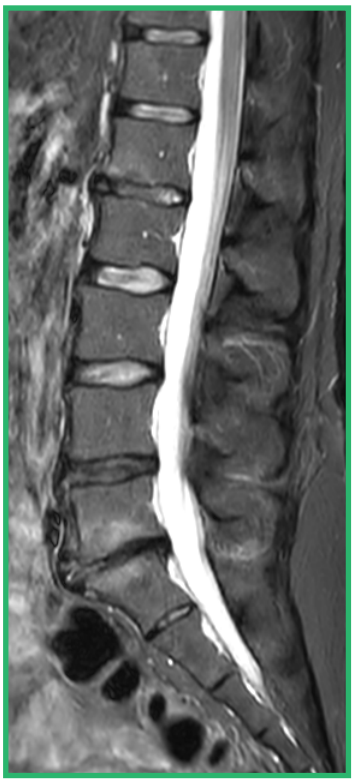
Precontrast T1



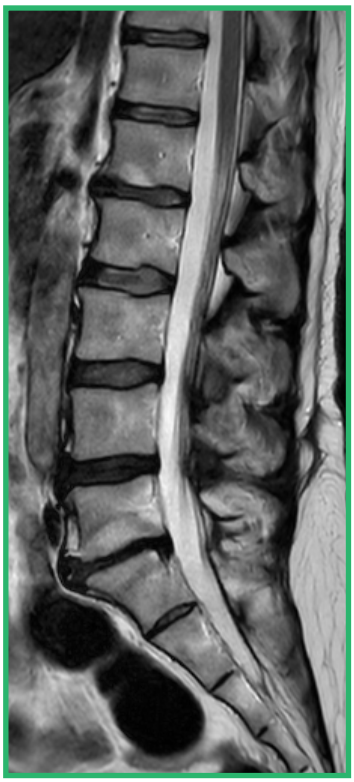
Proton density



STIR



T2



- **Noncontrast images demonstrate loss of disc height with mixed endplate region signal changes and loss of disc height at L4-L5**

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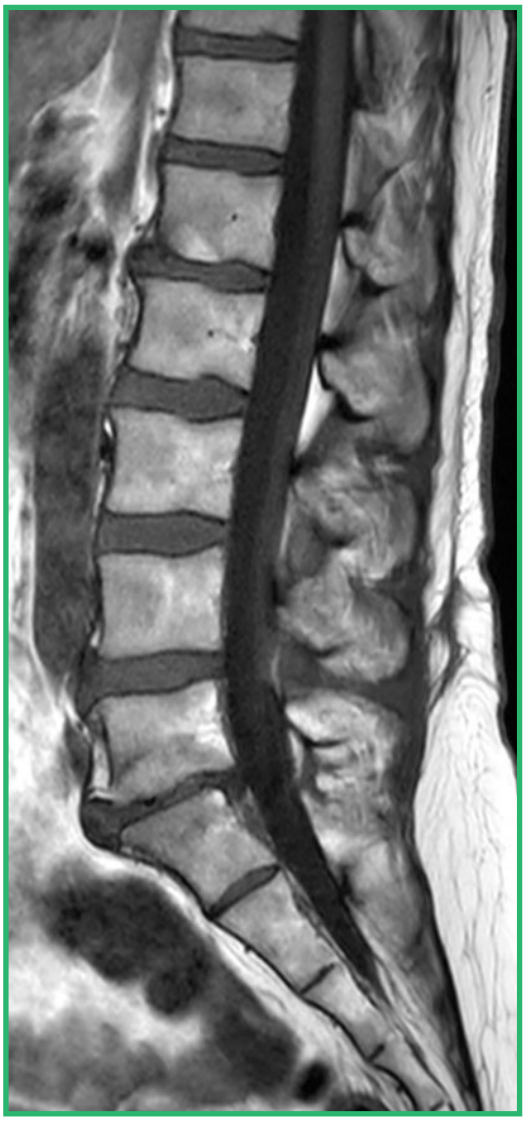
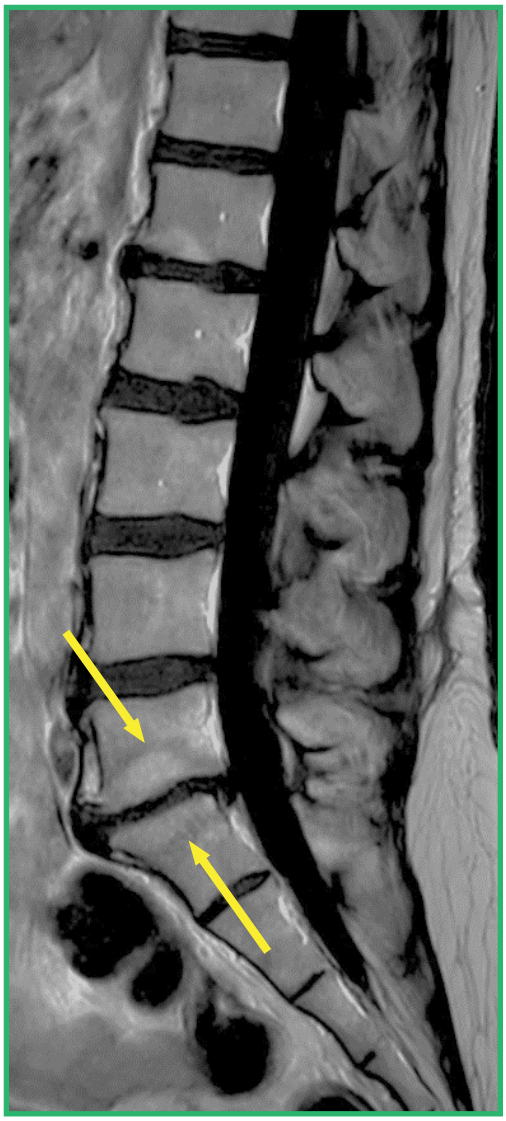
Case Study 5 (cont'd)

Precontrast T1



Postcontrast T1



- **Loss of disc height with mixed endplate region signal changes and enhancement**

Imaging Findings

Loss of disc height with mixed endplate region signal changes and enhancement which may be clinically symptomatic

Diagnosis

MRI results are consistent with symptomatic degenerative endplate changes

Treatment Plan

Conservative treatment and physical therapy

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Clariscan™
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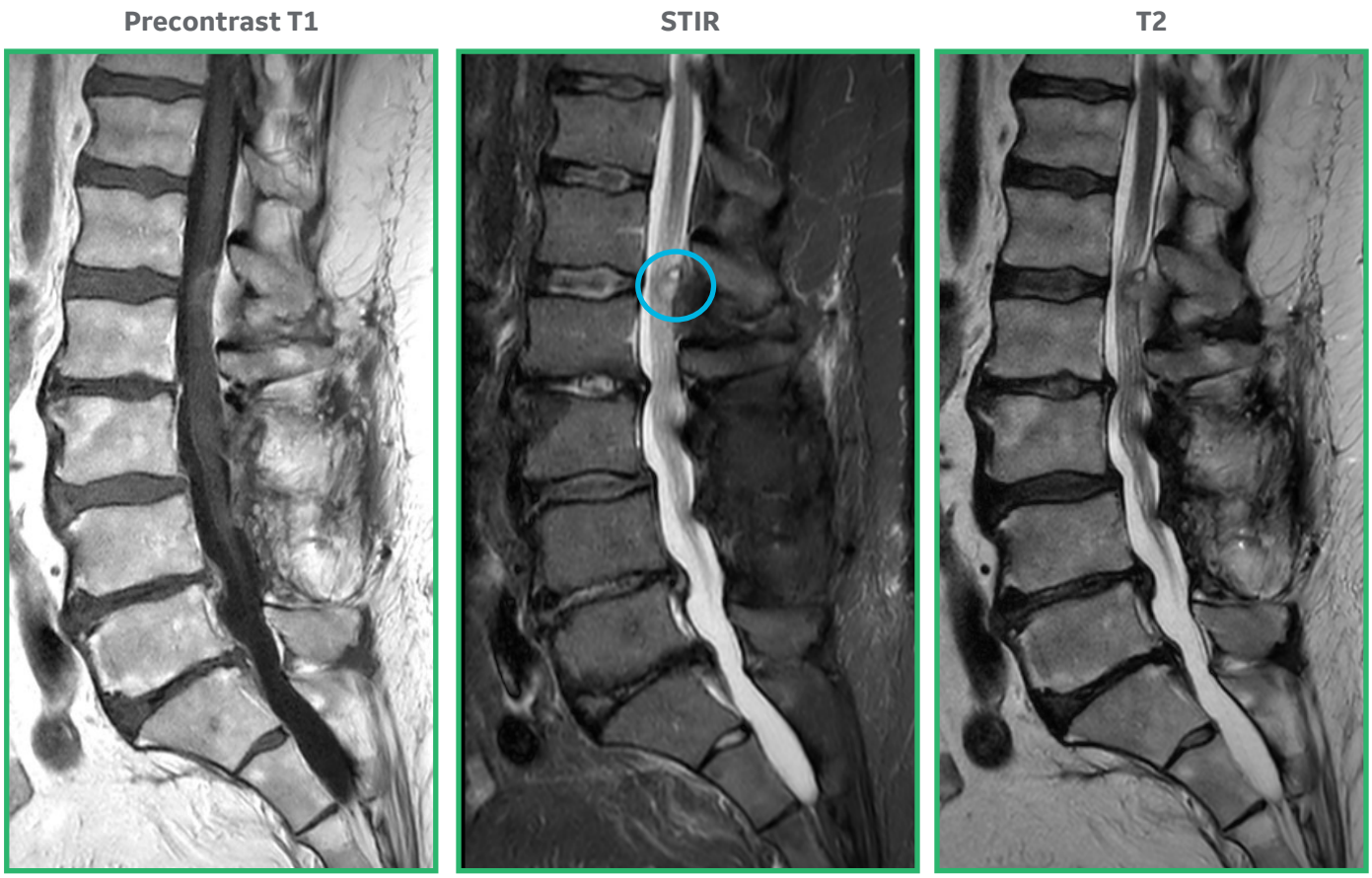
Case Study 6

Patient Presentation
62-year-old male weighing 200 lbs, presented with back pain

Imaging Plan
MRI of the spine with and without 20 mL of Clariscan™ (gadoterate meglumine)



- **Dorsal extradural lesion at L1-2 indenting the thecal sac (circle)**

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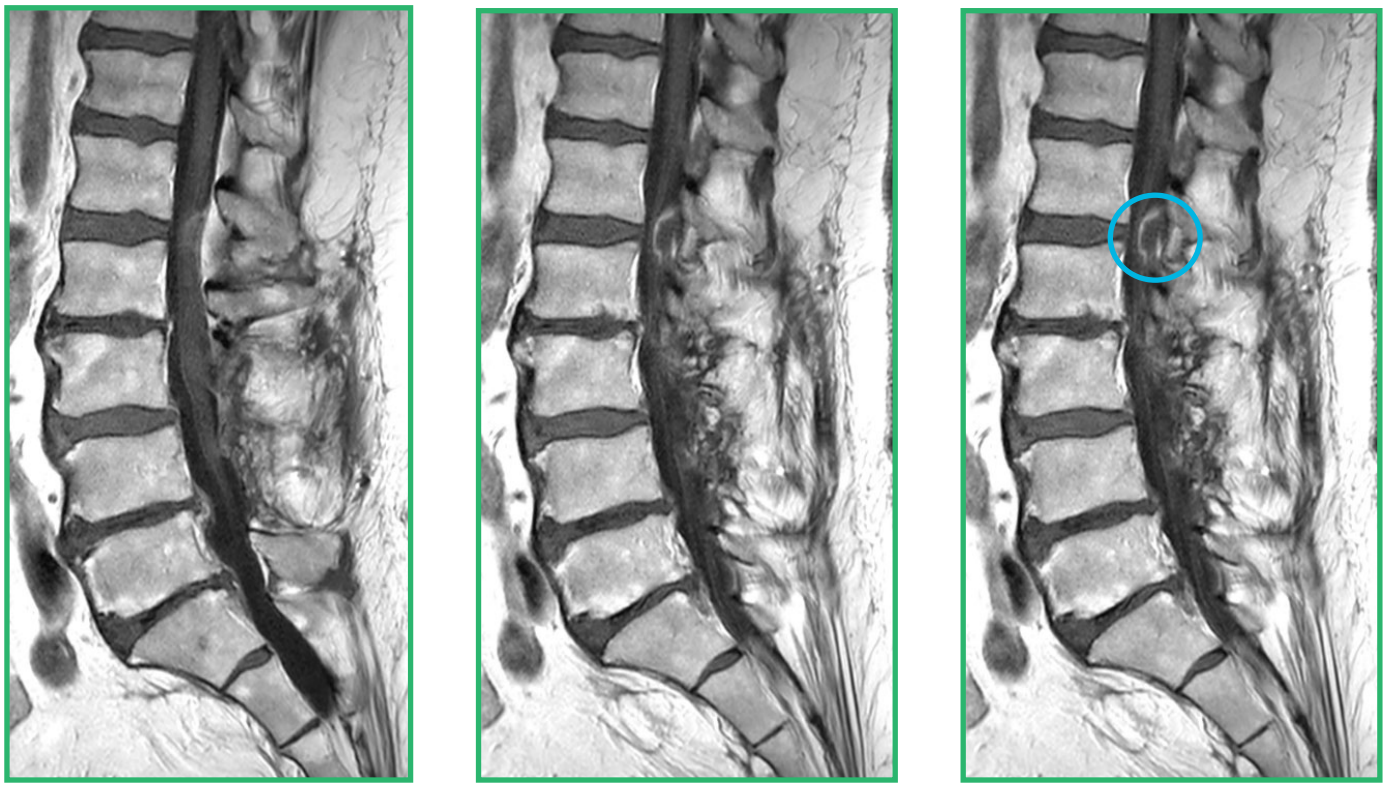
Case Study 6 (cont'd)

Precontrast T1 — Postcontrast T1



- **Peripherally enhancing dorsal extradural lesion at L1-2 indenting the thecal sac**

Imaging Findings
Peripherally enhancing dorsal extradural lesion at L1-2 indenting the thecal sac

Diagnosis
MRI results are consistent with synovial cyst

Treatment Plan
Resection

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Clariscan™
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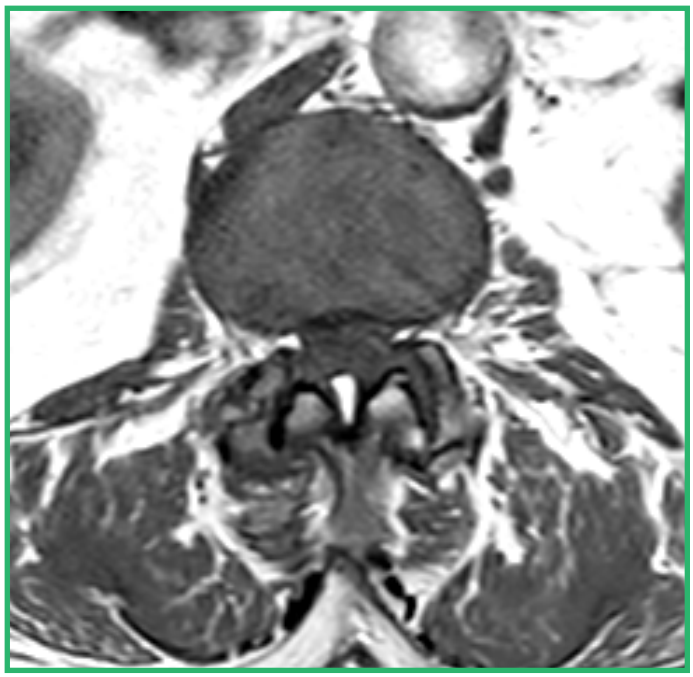
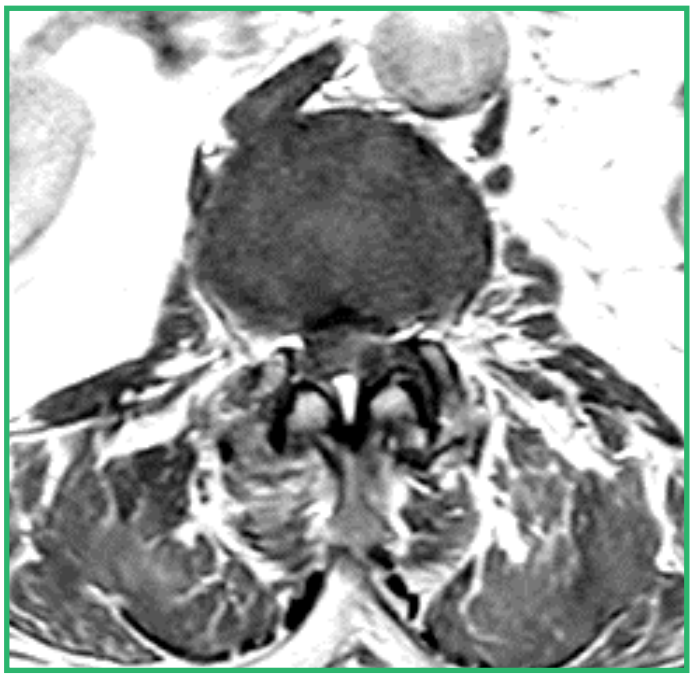
Case Study 6 (cont'd)

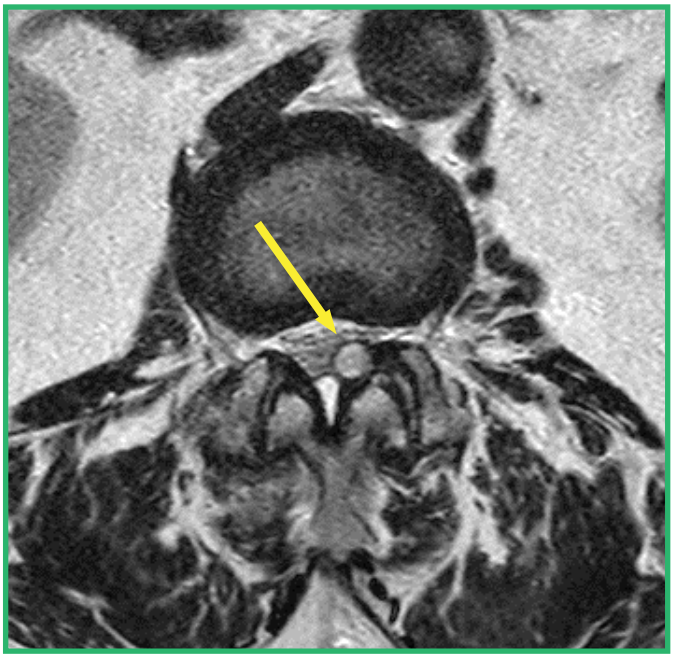
Precontrast T1



Postcontrast T1



Noncontrast T2



- Left sided dorsal extradural lesion at L1-2 indenting the thecal sac consistent with a facet joint synovial cyst

All case study images courtesy of Lawrence N. Tanenbaum, MD FACR and RadNet Inc.

Support for Clariscan

GE Healthcare Reimbursement Support Line

GE Healthcare is pleased to offer toll-free customer support and documentation for coding and reimbursement related to our products. Please contact us at 800 767 6664.

Customer Service

To place an order, call 800 292 8514.

Medical Affairs

For technical or product-related questions and/or to reach a Clinical Applications Specialist, call 800 654 0118 (option 2, then option 3) or email medical.affairs@ge.com.

*Dr. Tanenbaum is a consultant of GE Healthcare.

References:
1. Tweedle MF et al. *App Radiol.* 2014;(suppl):1-11.
2. Port M et al. *Biometals.* 2008;21:469-490.
3. Morcos SK. *Eur J Radiol.* 2008;66:175-179.

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Clariscan™
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injection for intravenous use

PRODUCT INDICATIONS AND USE:
CLARISCAN™ (gadoterate meglumine) is a gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine, and associated tissues in adult and pediatric patients to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

Additional pediatric use information is approved for Guerbet LLC's Dotarem (gadoterate meglumine injection). However, due to Guerbet LLC's marketing exclusivity, this drug product is not labeled with that pediatric information.

IMPORTANT SAFETY INFORMATION ABOUT CLARISCAN™

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
See full Prescribing Information for complete Boxed Warning.

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle, and internal organs.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR <30 mL/min/1.73 m^2), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **For patients at highest risk for NSF, do not exceed the recommended Clariscan dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.**

Contraindications
History of clinically important hypersensitivity reactions to Clariscan.

Warnings and precautions
- **Hypersensitivity reactions:** Anaphylactic and anaphylactoid reactions have been reported with gadoterate meglumine, involving cardiovascular, respiratory, and/or cutaneous manifestations. Some patients experienced circulatory collapse and died. In most cases, initial symptoms occurred within minutes of gadoterate meglumine administration and resolved with prompt emergency treatment.
  - Before Clariscan administration, assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders. These patients may have an increased risk for a hypersensitivity reaction to Clariscan.
  - Administer Clariscan only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation.
- **Gadolinium retention:** Gadolinium is retained for months or years in several organs. The highest concentrations have been identified in the bone, followed by brain, skin, kidney, liver and spleen. The duration of retention also varies by tissue and is longest in bone. Linear GBCAs cause more retention than macrocyclic GBCAs.
  - Consequences of gadolinium retention in the brain have not been established. Adverse events involving multiple organ systems have been reported in patients with normal renal function without an established causal link to gadolinium retention.
- **Acute kidney injury**: In patients with chronically reduced renal function, acute kidney injury requiring dialysis has occurred with the use of GBCAs. The risk of acute kidney injury may increase with increasing dose of the contrast agent; administer the lowest dose necessary for adequate imaging.
- **Extravasation and injection site reactions:** Ensure catheter and venous patency before the injection of Clariscan. Extravasation into tissues during Clariscan administration may result in tissue irritation.

Adverse reactions
- The most common adverse reactions (≥ 0.2%) associated with gadoterate meglumine in clinical trials were nausea, headache, injection site pain, injection site coldness and rash.
- Serious adverse reactions in the postmarketing experience have been reported with gadoterate meglumine. These serious adverse reactions include but are not limited to: arrhythmia, cardiac arrest, respiratory arrest, pharyngeal edema, laryngospasm, bronchospasm, coma and convulsion.

Use in specific populations
- **Pregnancy:** GBCAs cross the human placenta and result in fetal exposure and gadolinium retention. The human data on the association between GBCAs and adverse fetal outcomes are limited and inconclusive. Because of the potential risks of gadolinium to the fetus, use Clariscan only if imaging is essential during pregnancy and cannot be delayed. Advise pregnant women of the potential risk of fetal exposure to GBCAs.
- **Lactation:** There are no data on the presence of gadoterate in human milk, the effects on the breastfed infant, or the effects on milk production. However, published lactation data on other GBCAs indicate that 0.01 to 0.04% of the maternal gadolinium dose is present in breast milk.
- **Pediatric use:** The safety and efficacy of gadoterate meglumine at a single dose of 0.1 mmol/kg has been established in pediatric patients from 2 to 17 years of age based on clinical data in 133 pediatric patients 2 years of age and older. Adverse reactions in pediatric patients were similar to those reported in adults. No dosage adjustment according to age is necessary in pediatric patients. No cases of NSF associated with gadoterate meglumine or any other GBCA have been identified in pediatric patients age 6 years and younger. The safety of gadoterate meglumine has not been established in preterm neonates.

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Prior to Clariscan administration please read the full Prescribing Information, including the Boxed Warning and patient Medication Guide, for additional important safety information.

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 800-654-0118 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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