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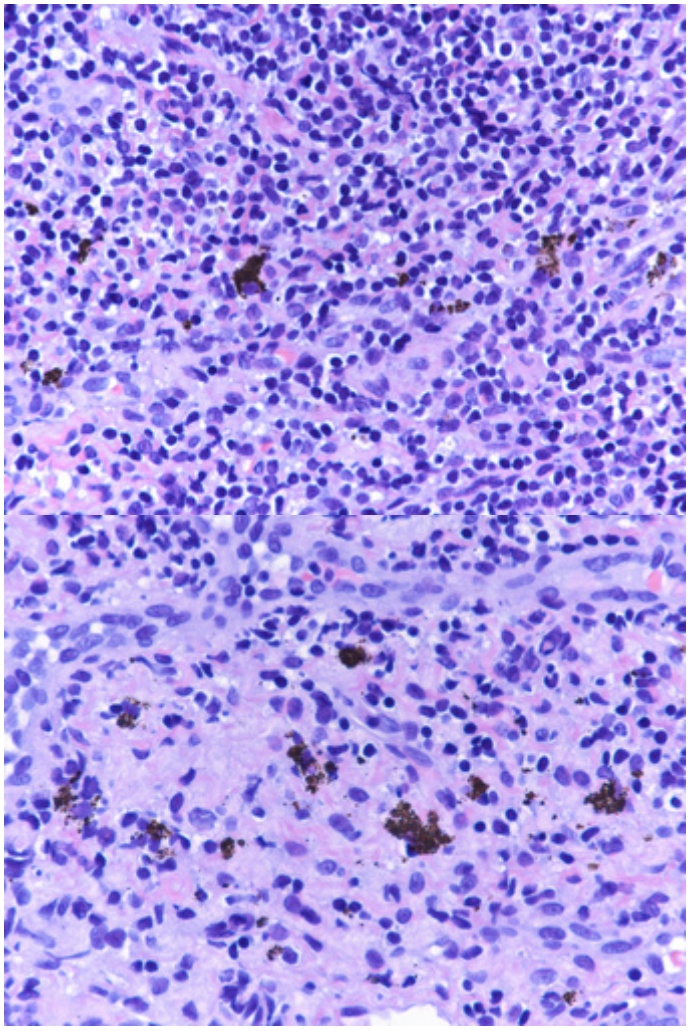
Ileum biopsies in a 16-year-old male.

What is your diagnosis?



Diagnosis:

Titanium dioxide nanoparticles (Peyer’s patch pigment).

Comment:

The terminal ileum biopsy shows deposition of fine textured, dark- brown pigments within the cytoplasm of the macrophages in the Peyer’s patches of the ileum (Panel A and B). No granulomatous inflammation, multinucleated giant cell formation or malignant cells are observed.

These exogenous pigments in the Peyer’s patches was first described in Human Pathology by Neil A. Shepherd in 1987. Although titanium deposition is unique to the terminal ileum, it can also be found in the mesenteric lymph nodes and transmural inflammatory aggregates of Crohn’s disease. This pigment is fine in texture, dark- brown- to black in colour and confined to the cytoplasm of macrophages. Historical studies using scanning electron microscopy, backscattered electron imaging and X-ray energy spectroscopy of routine histologic sections determined that these pigments represent titanium, aluminium and silicon. Currently this pigment is simply referred to as titanium.

Titanium dioxide is one of the most produced nanoparticles worldwide and is commonly used in daily consumer products as food additive, whitening agents in confectionary (tooth paste, chewing gum and candies), white sauces and icing. The ingested particles are deposited within the lymphoid aggregates of the terminal ileum (Payer's patches) via routine immunosurveillance -related trafficking.

Some animal studies have shown that titanium dioxide causes adverse effect via induction of oxidate stress resulting in cell damage, genotoxicity and inflammation. In the bowel, titanium dioxide has the ability to disrupt intestinal barrier and induce intestinal inflammation via production of reactive oxygen species (ROS). The International Agency for Research on Cancer (IARC) has listed titanium dioxide as a Group 2B carcinogens as animal studies has linked its inhalation to lung tumour development. However, no reliable data or research has shown that titanium dioxide in food harms human health.

The differential diagnosis for titanium pigment deposition includes:

i) Hemosiderin pigment deposition (resulting from intermittent bleeding from upper gastrointestinal tract) which is highlighted by Prussian blue stain.

ii) Intestinal lipofuscinosis (light brown granular pigments deposited within the smooth muscle cells of muscularis mucosae, muscularis propria and macrophages), highlighted by PAS or Masson – Fontana special stain.

iii) Tattoo pigment used for preoperative tattooing can be easily mistaken for Titanium since both are dark-brown and distributed within the cytoplasm of macrophages (useful clues: these pigments are very prominently distributed and not restricted to terminal ileum).

iv) Formalin pigment (tissue artifact) is not seen within the macrophages and is not even on the same plane as the examined tissue.

v) Melanin pigment is variably course, brown and is within the cytoplasm of overtly malignant cells, highlighted by Melan A, SOX 10 and other melanoma markers. In conclusion, although most studies to date show no harmful effects of titanium dioxide consumption, there is still no long-term human studies on dietary titanium dioxide available. Therefore, a more cautious use of this particle is recommended.

For further reading:

- Neil A. Shepherd, David A. Levinson, Exogenous pigment in Peyer 's patches. Human Pathology. 1987;1: 50-4
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- Freeman HJ, "Melanosis" in the small and large intestine. World Journal of Gastroenterology. 2008; 14: 4296-99
- Feroze N. Ghadially, Virginia M. Walley, Pigments of the Gastrointestinal Tract: A Comparison of Light Microscopic and Electron Microscopic Findings. Ultrastructural Pathology. 2009; 19: 213-9
- Matej Skocaj, Metka Filipic, Jana Petkovic, Sasa Novak, Titanium dioxide in our everyday life; is it safe? Radio Oncol. 2011; 45: 227-47

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