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Case Report

Phosphoglyceride crystal deposition disease involving adnexa uteri: a case report with histogenetic consideration

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Summary

We present a rare case of phosphoglyceride crystal deposition disease (PCDD), as a gynecologic disease, with reference to histogenesis of crystal deposition. An 84-year-old woman, who had undergone simple hysterectomy for uterine leiomyoma 44 years previously, presented with multiple masses in the bilateral adnexa and the pelvic wall. The bilateral adnexal tumors were resected. The masses histologically revealed a foreign-body granuloma composed of numerous tiny, radially arranged needle-like crystal lumps surrounded by multinucleated giant cells and macrophages. The crystals showed birefringence under polarized light and were positive for gold hydroxamic acid stain, and the tumor was thus diagnosed as PCDD. The masses revealed central cystic changes due to old hemorrhage, which contained crystal lumps without foreign-body reaction or birefringence. The present case demonstrated for the first time that phosphoglyceride crystals developed in old hemorrhagic foci, although it was not confirmed whether the old hemorrhagic foci were formed after hysterectomy or due to endometriosis.

Key words: phosphoglyceride crystal deposition disease, foreign-body granuloma, birefringence, gold hydroxamic acid stain, old hemorrhage

Introduction

Phosphoglyceride crystal deposition disease (PCDD) is defined as the deposition of crystals of phosphoglyceride (PG) and clinically exhibits soft tissue mass reminiscent of neoplasm [1-10]. The PG crystals are characterized by refringence under polarized light and positive staining by the gold hydroxamic acid (GHA) method[11]. PCDD is extremely rare and usually develops at the site of surgical incision or that of repeated injections on the body surface [1-3,9] as well as in internal organs [4-8,10]. These facts suggest the role of tissue injury in the deposition and formation of PG crystals [1]. However, the histogenesis and molecular mechanism of PCDD are yet to be clarified.

In the present report, we describe a case of PCDD in the uterine adnexa and the pelvic wall, suggesting that the crystals were separated from old hemorrhagic foci. We believe that this case is valuable in elucidating the histogenesis of PG crystal deposition.

Clinical summary

An 84-year-old Japanese woman, who had undergone total hysterectomy with adnexal preservation for uterine leiomyoma about 44 years

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Conflict of interest
The Authors declare no conflict of interest.

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previously, had abnormal shadow in the upper lobe of the left lung during a medical checkup. The lesion was diagnosed as pulmonary adenocarcinoma by bronchial brushing cytology. Computed tomography and magnetic resonance imaging for general examination showed several masses in the bilateral adnexa and on the pelvic wall, and it was not confirmed whether these tumors were metastatic carcinoma or primary tumors. She underwent a laparoscopic resection of bilateral adnexal tumors. During the operation, five nodular tumors were noted in the pelvic cavity. There were two nodules, 3 cm and 4 cm in diameter, replacing the bilateral adnexa, and the right-sided tumor contained a normal-looking ovary and tubal fimbria just adjacent to the tumor. The other three nodules, which were not extirpated, were located on the posterior peritoneal surface of the urinary bladder (one nodule, 4.5 cm in diameter) and the vaginal stump (two nodules, 1.5 cm in diameter, respectively). After the tumors were confirmed to be non-neoplastic lesions, the patient received chemotherapy for lung cancer and remained in a stable state.

Pathological findings

The resected adnexal tumors were approximately 4.0 × 3.0 × 1.5 cm (left) and 5.0 × 4.5 × 3.2 cm (right) in size and both were replaced by yellowish-brown tumors (Fig. 1A). Ovarian and tubal tissues were present just adjacent to the right-sided tumor (Fig. 1B), where small lesions of endometriosis, confirmed by immunohistochemistry for CD10, showing the presence of endometrial stroma, were observed (Figs. 1 C, 1 D). On the cut surface, both were yellowish-brown, solid tumors with central cystic changes (Figs. 1 B, 2A). Histologically, both tumors were composed of foreign-body granulomas; there were numerous tiny basophilic or eosinophilic masses of needle-like crystals, approximately 50 to 150 μm in diameter, arranged radially from the center and surrounded by foreign-body type giant cells (GCs) and macrophages (Figs. 2B, 3B). These crystal lumps showed birefringence under polarized light (Figs. 2C, 3C, 4A) and were positively stained by the GHA method[11] (Fig. 4B), indicating that the masses were PG crystals. Some GCs phagocy-

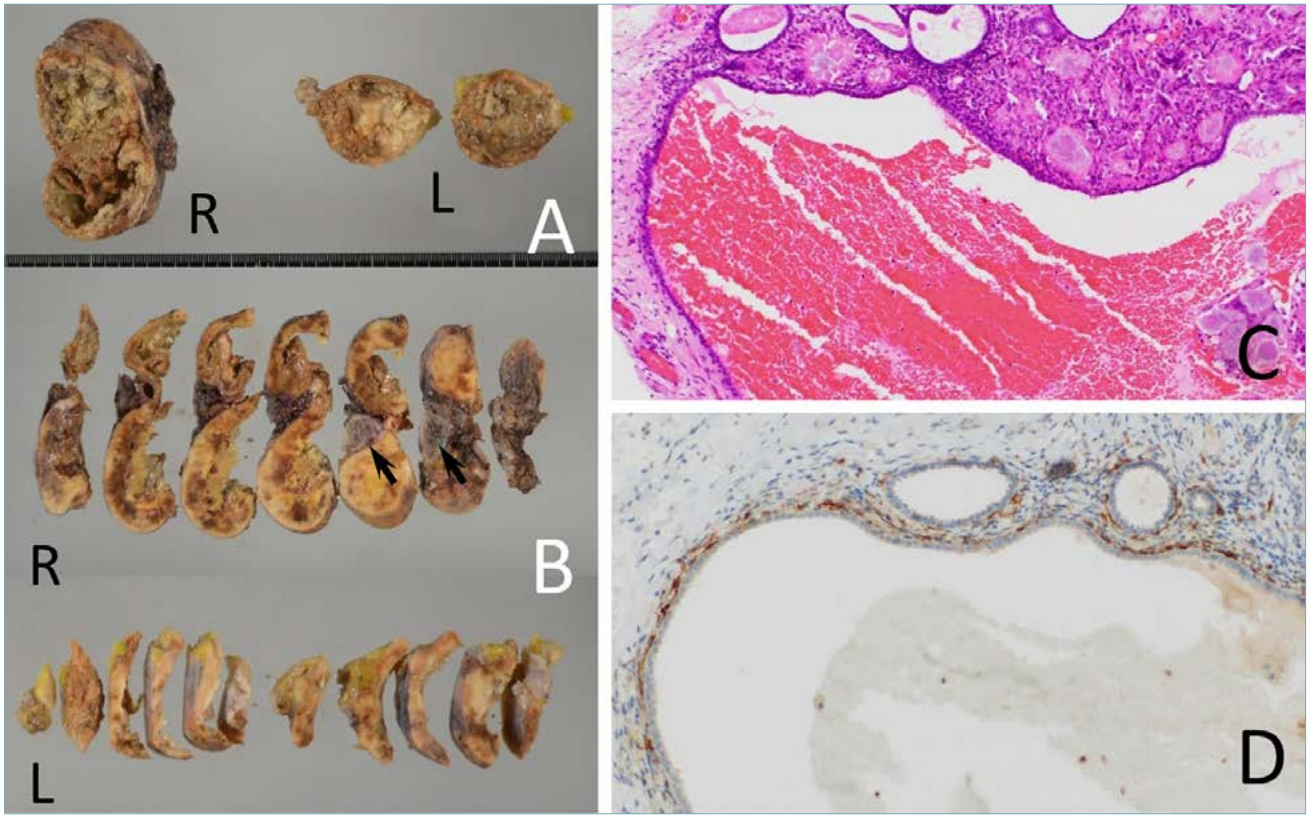

Figure 1. (A)(B) Gross appearance/cut surface of adnexal lesions (L: left, R: right), showing yellowish-brown, solid tumors with central cystic changes (arrows: ovary just adjacent to the tumor); (C)(D) Endometriosis of the right adnexa just adjacent the tumor. Endometrial stroma, immunoreactive for CD10, is observed in peri-glandular area (D).

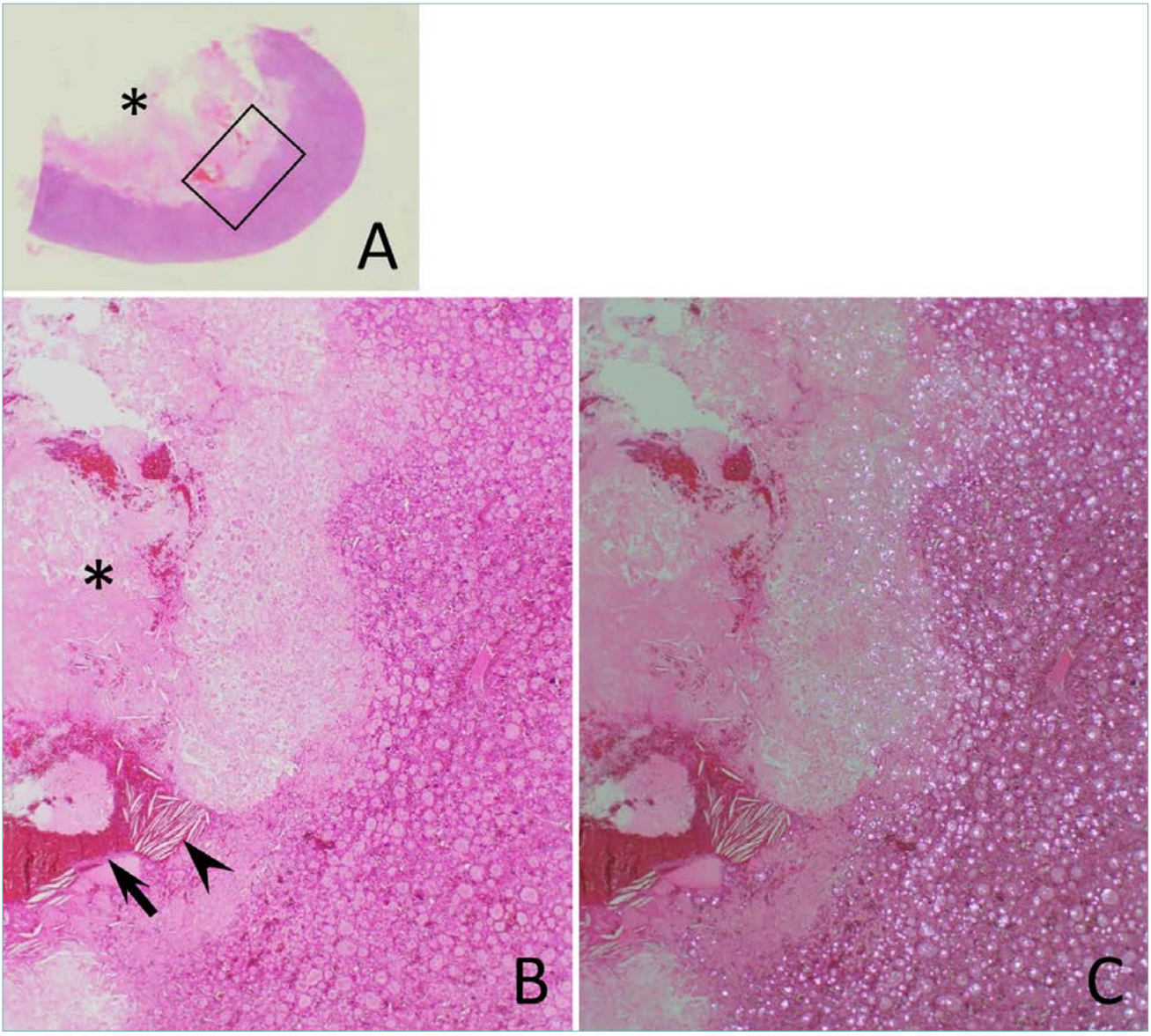

Figure 2. Low-power view of the resected tumor (H.E. stain, (C): view under polarized light). (A) Loupe image of the tumor, showing cystic changes in the central region (asterisk); (B)(C) Magnification of the square in (A), showing numerous tiny nodular lesions surrounding old (asterisk) and fresh (arrow) hemorrhagic foci containing cholesterin crystals (arrowhead). Under polarized light, the nodular lesions in the peripheral area contain refractile crystals, whereas, in the center of the lesion, they tend to show no birefringence (C).

tosed minute crystal lumps and contained asteroid bodies (ABs) (Fig. 3D), the latter being not refractile under polarized light. Intracytoplasmic crystal lumps and ABs were histologically similar, except that the latter contained eosinophilic amorphous material in the center. Among granulomatous lesions, hemosiderin deposition or hemosiderin-laden macrophages were observed (Fig. 4F).

The central region of the tumor showed cystic changes and contained amorphous old hemorrhagic foci intermingled with fresh hemorrhage, cholesterin crystals and fibrinous exudate (Fig. 2B). Among old hemorrhagic foci, there were many tiny radiating crystals without foreign body reaction (Fig. 3A), and these showed a transition to those with foreign-body reaction (Figs. 2B, 2C). Some of these crystals were neither refractile under polarized light nor positive for GHA, while birefringent/GHA-positive crystals were

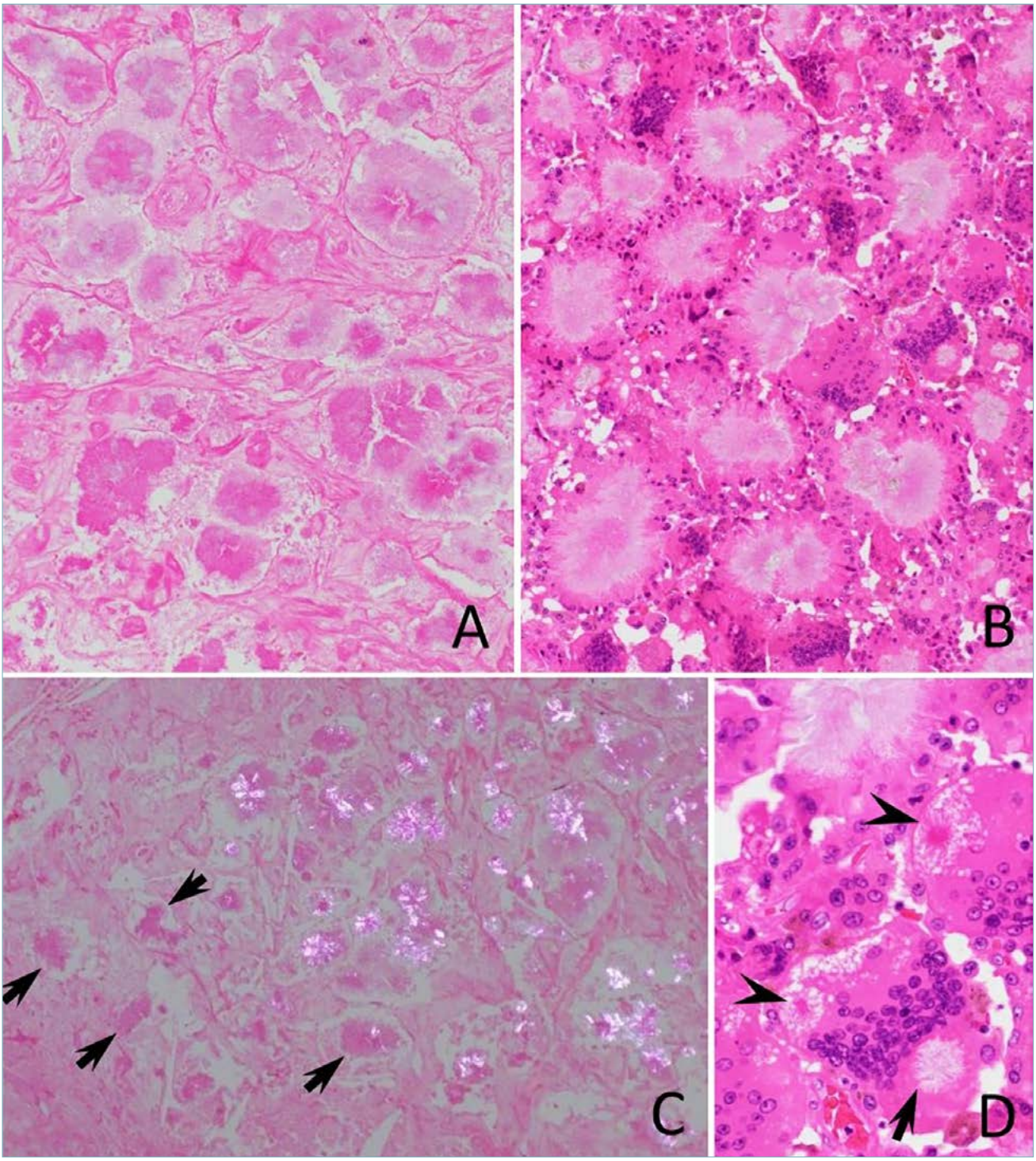

Figure 3. Histology of the resected tumor (H.E. stain, (C): view under polarized light). (A)(B) Needle-like crystal lumps without foreign-body reaction in the center of the lesion (A) and with foreign-body reaction in the peripheral area (B); (C) A transition from the lumps without birefringence (arrows) to those with birefringence; (D) Some foreign-body giant cells phagocytose minute crystal lump (arrow) and contain asteroid bodies (arrowheads).

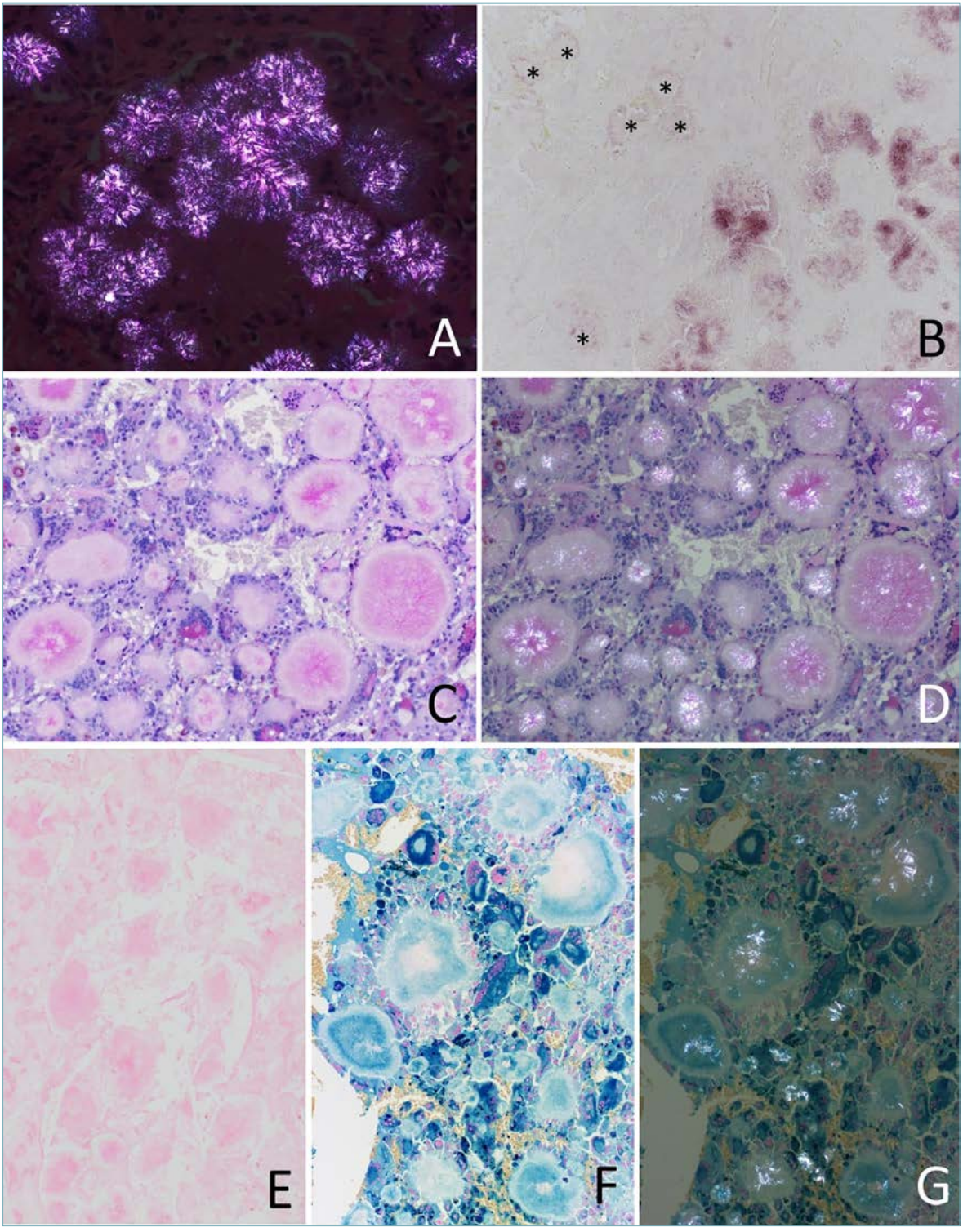

Figure 4. (A) Under polarized light observation, the crystal masses in the peripheral region of the tumor are composed of numerous refractile, needle-like crystals, arranged radially from the center; (B) The crystals masses in the peripheral region of the tumor are positively stained by gold hydroxamic acid method, while those in the center of the tumor are negative or weakly positive (asterisks); (C)(D) Diastase-periodic acid-Schiff (dPAS) stain/ (E)-(G): Prussian blue stain ((D)(G): under polarized light), showing no hemosiderin deposition in the crystal lumps without foreign body reaction (E) and refractile crystals are negative for dPAS (C)(D) or Prussian blue (F)(G).

gradually prominent towards the periphery of the tumor (Figs. 3C, 4B), where many foreign-body granulomas were present.
The crystals were partially positive for diastase-periodic acid-Schiff (dPAS) (Fig. 4C) and Schmorl stain, but negative for Luxol fast blue stain. The Prussian blue stain highlighted some, but not all, hemosiderin-laden macrophages and crystal lumps with foreign body reaction (Fig. 4F), whereas did not those without foreign body reaction (Fig. 4E). The refractile crystals were negative for dPAS or Prussian blue (Figs. 4D, 4G).

Discussion

PCDD is extremely rare; to the best of our knowledge, only 12 cases, all from Japan, have been reported to date [1-10]. In 10 of these cases, the lesions developed at the site of postoperative scar or repeated injections on the body surface (abdominal wall [1,3,9], buttock [2] and upper arm [3]) as well as in internal organs (peritoneum [4], spine [5], anterior mediastinum [6,8], cardiac wall [10], and pelvic wall [7]) a long time (20-45 years) after operation/injection. These findings suggest that tissue injury may play an important role in PG deposition, while its developmental process is still largely unknown.
The present case is quite valuable in that its histology clarifies the histogenesis of crystal deposition. The crystal lumps in old hemorrhagic foci in the cystic part of tumors were not surrounded by macrophages/GCs, neither were they refractile under polarized light. These findings indicate that PG crystals separated from old hemorrhagic foci in the center of tumors, although it is not clear whether old hemorrhagic foci in the tumor are due to endometriosis or surgical procedures for total hysterectomy performed 44 years ago. Some authors speculated that local disturbance of PG metabolism *within* macrophages is initiated by local inflammation and undigested material accumulates and crystallizes [1,4,7,9], whereas, in the present case, the foreign-body reaction seems to be a secondary change against the deposited PG crystals. In the previously reported cases also, the tumors showed cystic changes in the center in three cases [1,2,7]; one contained old hematoma [2] and the other had necrotic tissue, fibrinous exudate and cholesterin crystals [7]. It is possible that PG crystal deposition developed in old hemorrhagic foci in these cases, although the authors did not mention about it.
As old hemorrhagic foci contain numerous destructed/degenerative cell membranous components of erythrocytes, it is suggested that, in the present case, phospholipids released from cell membranes were crystallized. ABs in GCs, showing structures similar to minute PG crystal lumps phagocytosed by GCs, also support this hypothesis, because it has been reported that ABs are composed of membrane phospholipid bilayers [12,13]. The crystal lumps were also positive for dPAS, Schmorl and Prussian blue staining in part, whereas refractile crystals were negative by these methods. In addition, Prussian blue staining partially highlighted hemosiderin-laden macrophages as well as some crystal lumps surrounded by macrophages/GCs, while the crystal lumps without foreign body reaction were negative, suggesting that hemosiderin deposition in the crystals was associated with granuloma formation. These findings indicate that components such as carbohydrates, lipofuscin, and hemosiderin are not indispensable for crystallization.
As PG itself does not make crystal structures [3], some factor(s) may be essential for crystallization. Although *in vitro* studies indicate crystallization of phospholipids develops in association with phase transition and phase organization [14], it is not obvious what kind of condition *in vivo* crystallization is caused under. The initiating factor(s) of PG crystal deposition after hemorrhage and the detailed mechanism of crystallization remain to be elucidated, while it might be possible that something such as drugs or foreign substances mingled at the surgical sites worked as an initiating factor for PG crystallization. Considering that all of the reported cases are from Japan [1-10], this assumptive agent(s) might be used or was present in the past in Japan, although it has not been identified until now. We know a similar example, mesenteric phlebosclerosis, that is predominantly found in Japan; it was first described as a disease with unknown cause [15], and was revealed later to develop by herbal medicine [16,17]. Therefore, in case reports of PCDD in the future, medication history and/or detailed surgical situation should be investigated thoroughly.

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Ethical aspect

This work was approved by an institutional ethical review board at Ina Central Hospital (Ina, Japan).

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