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Total laparoscopic curative resection of a rare pan-necrotic solid pseudopapillary pancreatic tumor in a child

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Abstract:

Tumor necrosis is purportedly related to an aggressive tumor phenotype in few solid tumors such as pancreatic ductal carcinoma, breast and bladder carcinomas. We hereby report a unique pan-necrotic (98% of tumor) pseudopapillary pancreatic tumor in a 13-year-old child who underwent laparoscopic subtotal pancreatectomy and curative resection. To our knowledge, this is the first account of complete tumor necrosis in a pancreatic neoplasm with curative laparoscopic resection. This case report has discussed the literary background of various mechanisms of cell death in solid tumors to explain the plausible cause of unique pan-tumor necrosis.

Keywords:

Child, laparoscopic subtotal pancreatectomy, necroptosis, pan-necrosis, pseudopapillary pancreatic tumor, tumor hypoxia

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Introduction

Angiogenesis is critical for tumor growth. Foci of cell death are commonly observed in core regions of solid tumors because of inadequate vascularization and subsequent metabolic stresses such as hypoxia and nutrient deprivation.[1] Because the morphology of dead tumor cells appears to be necrotic, these foci of cell death are referred to as tumor necrosis.[2] Tumor necrosis is often associated with aggressive tumor development and metastasis and is thought to be an indication of poor prognosis in patients with breast, lung, and kidney cancer.[1,2] Previous studies have shown that metabolic stresses such as hypoxia, glutamine, or glucose deprivation could trigger apoptotic, autophagy-dependent, or necrotic cell death in cancer cells.[3]

Unlike rapidly growing malignant tumors, benign tumors do not commonly show extensive tumor necrosis. Hypoxia, nutrient deprivation, or other metabolic stresses are not as profound as in aggressive malignant and chemotherapy-subjected tumors. Cell death in tumors has been extensively studied in recent years, suggesting several modes of cell death in tumors including programmed, regulated, unregulated, and random types of cellular deaths such as apoptosis, necrosis, necroptosis, pyroptosis, and ferroptosis.[4-6]

There has been no reported case of pan-tumor necrosis in pancreatic neoplasia (malignant and benign) hitherto in the literature. We discuss the presentation, imaging findings, surgical management, and plausible explanation for this rare and unique histopathology in a child.

Case Report

A 13-year-old girl presented with lingering back pain for 2-month duration, worsened

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for 1 week associated with postprandial discomfort, nausea, occasional fever, and vomiting during her recent holiday. Upon evaluation, she was found to have anemia, a large solid tumor in the body of the pancreas on ultrasound, normal amylase, lipase, and CA 19-9 levels. Contrast computed tomography abdomen revealed a poorly enhancing, well-circumscribed solid mass measuring 11 cm × 9 cm × 6 cm in the body of the pancreas abutting to mesenteric-portal confluence [Figure 1]. There was no evidence of local invasion or distant radiologically discernable metastasis in the liver, peritoneum, pelvis, and ovaries. After a thorough discussion with the parents regarding high prospects of a curative resection with possible concurrent splenectomy, consent for the same was obtained. The child was prepared with preoperative pneumococcal and meningococcal vaccination 2 weeks before the surgery. A laparoscopic resection of tumor was carried out involving subtotal pancreatectomy and splenectomy. The spleno-mesenteric-portal vein confluence could be dissected off the tumor margin at a safe distance [Figure 2]. The postoperative recovery was smooth with minimal requirement of analgesia, early return to activity, resumption of full feed in 36 h (short period of gastroparesis), and discharge on the 3rd postoperative day. Follow-up showed moderate thrombocytosis managed with oral hydration and aspirin. The child is on a regular diet and passing 1–2 bowel motions per day (no sign of malabsorption) with a maintained blood sugar level.

The gross and histologic section shows near complete necrotic(approximately98%)[Figures 3 and 4], well-circumscribed solid pseudopapillary tumor with foci of hemorrhage, cholesterol clefts, and minimal foci of atypical epithelioid cells showing some solid nests of cohesive cells forming a cuff surrounding blood vessels creating a pseudopapillary architecture. Stroma showed focal hyalinization, fibrosis, and histiocytic aggregates. Inflammatory cells are minimal. Tumor cells showed a moderate amount of eosinophilic cytoplasm with rare/vague intracytoplasmic globules and perinuclear vacuoles, uniform looking nuclei with finely textured chromatin inconspicuous nucleoli and occasional grooves [Figures 5-7]. Tumor is confined to the pancreas, negative for lymphovascular or perineural invasions. Surrounding the tumor is normal viable looking pancreatic tissue with distinct demarcation between necrotic tumor and viable pancreatic tissue. All surgical resection margins were negative for tumor or atypia.

Immunohistochemical stains show tumor cells expressing CD10 [Figure 8], beta-catenin (focal and nuclear staining), and cyclin D1 [Figure 9] (weak, 10%–20% of tumor volume) [Figure 3]. They are negative for CKAE1/AE3, vimentin, progesterone, SOX11, and synaptophysin.

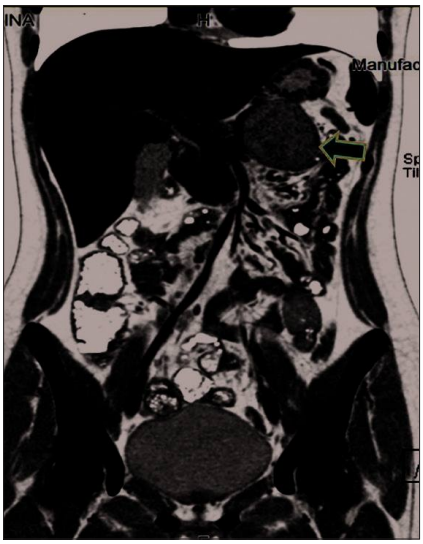

Figure 1: Contrast computed tomography abdomen showing poorly enhancing pancreatic tumor (red arrow)

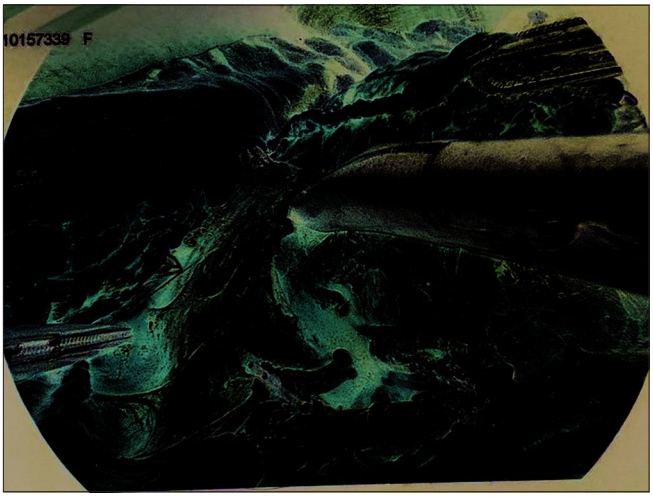

Figure 2: Intraoperative view of the tumor abutting spleno-porto-mesenteric vein confluence (blue arrow)

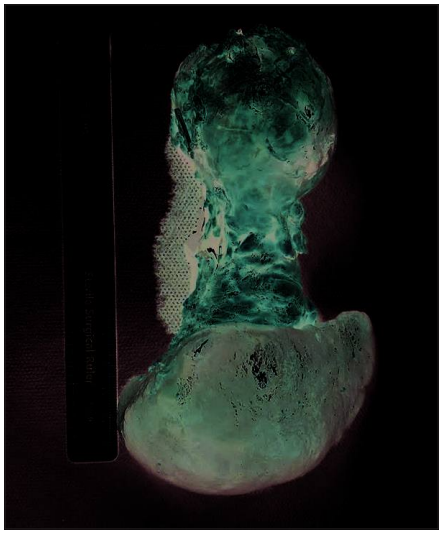

Figure 3: Subtotal pancreatectomy and splenectomy specimen delivery

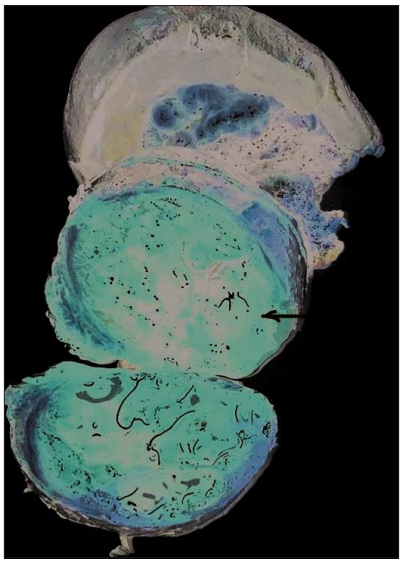

Figure 4: Cut-open view of necrotic core. Blue arrow depicts necrotic core

Figure 6: Histopathology - partially necrotic area showing cohesive cells forming a cuff around blood vessels creating a pseudopapillary architecture. Cells show a moderate amount of eosinophilic cytoplasm. Foci of cholesterol clefts also identified (blue arrow), 40x magnification. Blue arrow depicts Foci of cholesterol clefts

Figure 8: Staining with CD10 immunostains, 40x magnification

Figure 5: Histopathology - necrotic tumor with viable peritumoral pancreatic tissue, 40x magnification. Blue tissue depicts viable peritumoral pancreatic tissue

Figure 7: Histopathology showing complete necrotic tumor cells with ghost cells and intact membrane, 40x magnification. Blue arroow depicts necrotic tumor cells with ghost cells and intact membrane

Figure 9: Staining with cyclin D1 immunostains, 40x magnification

Discussion

Broadly, cell death can happen through either an active, regulated programmed cell death known as apoptosis or

a passive, uncontrolled course called necrosis. Apoptosis is defined as programmed cell death characterized by the activation of caspases, which are cysteine proteases that cleave cellular substrates, and the morphological features of cellular shrinkage, chromatin condensation, nuclear fragmentation, and membrane blebbing.[3,4] At the end of the apoptotic process, dying cells are broken into membrane-bounded bodies containing the cellular structures and organelles, known as apoptotic bodies, which are taken up by surrounding cells or by phagocytic cells of the immune system without triggering inflammation.[3-6] In contrast, necrosis is thought to be independent of the activity of caspases and is characterized by cellular swelling, organelle dysfunction, extensive mitochondrial damage, and plasma membrane rupture.[2-6] Because necrotic cells release their cell contents including proteins and nucleic acids, necrosis is much more inflammatory compared to apoptosis. Unlike apoptosis in which cells have intact membranes and are rapidly removed by host macrophages, it has been shown that tumor necrosis leads to the release of intracellular components to the tumor microenvironment.[2,6] A recent study found that a high level of potassium was released from necrotic tumor cells.[7] Importantly, this study suggests that the extracellular potassium released from tumor necrosis inhibits both CD4 and CD8 T-cell activities that are critical for antitumor immunity.[7]

Hypoxia is a common feature of human cancers, leading to cell death seen as necrosis. It induces a transcription program-mediated hypoxia-inducible factor-1a (HIF-1a) that promotes an aggressive tumor phenotype.[8-10] It is a prognostic indicator in many solid tumors[9] and is often detected by examining the expression of carbonic anhydrase IX (CAIX),[11] which is a regulator of cellular pH, and its expression is induced by HIF-1a.[8,10] Intratumoral hypoxia is reflected histologically by the presence of necrosis, which has also been reported to be a prognostic factor in patients with breast[12] and bladder[13] cancers. Hypoxia is evident in pancreatic ductal carcinomas (PDCs), in which expression of HIF-1a and CAIX has been detected in 60%–70% and 78% of cases, respectively,[14-17] whereas histological necrosis has been found in only 30%–40% of PDCs in previous studies.[17,18] A pan-tumor necrosis has never been reported hitherto in the literature.

In our case, there were an abundance of ghost cells with intact membrane and a paucity of inflammatory cells in the most part of the tumor, suggesting an alternate apoptotic mechanism of cell death.

In recent years, the concept of cell death has evolved dramatically because of the extensive studies of the role of cell death in normal tissue homeostasis and in the wide spectrum of diseases including autoimmune disease, neurodegenerative diseases, and cancer.[5,6] It is now accepted that there are other forms of programmed cell death such as pyroptosis and ferroptosis that are distinct. While engaging pyroptosis needs the activation of caspase-1, pyroptotic cell death leads to the rupture of plasma membrane and the release of cell contents, which results in the subsequent inflammatory responses.[5,6] Ferroptosis is a nonapoptotic, iron-dependent form of cell death.[5,6] More importantly, it has been found that necrosis could also happen in a programmed, finely regulated fashion under certain conditions. For instance, when apoptosis is blocked, tumor necrosis factor triggers certain types of cells to undergo a regulated necrotic cell death. This regulated necrosis is termed necroptosis.[3,19] Necroptosis is a form of programmed, caspase-independent necrosis and has all the morphological features of necrosis.[5,19] Necroptosis has originally been observed by studying death receptor-induced cell death, but it is clear now that necroptosis mostly happens under pathological conditions *in vivo*, such as viral infection.[6,19]

Conclusion

Tumor necrosis in solid tumors is multidimensional and multifactorial ranging across programmed apoptosis, random hypoxic/metabolic stress-induced necrosis, and regulated necroptosis. Tumor necrosis in benign tumors could be nonhypoxic and plausibly due to necroptosis which could lead to extensive cell death (pan-necrotic). Further studies would clarify the definitive etiology. Pan-tumor necrosis/necroptosis could purport a good prognosis and enable curative resection of pancreatic tumors more feasible by a minimally access approach in children with minimal blood loss.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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