Cytologic Features and Clinical Implications of Undifferentiated Carcinoma With Osteoclastic Giant Cells of the Pancreas: An Analysis of 15 Cases

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BACKGROUND: The cytologic features of undifferentiated pancreatic carcinoma with osteoclastic giant cells (UOC) are rarely described. **METHODS:** Cytologic and clinicopathologic characteristics in 15 UOC fine-needle aspiration (FNA) specimens were analyzed. **RESULTS:** FNA specimens were obtained from 6 men and 8 women with a mean age of 65 years who had UOCs (head, n = 7; body, n = 3; and tail, n = 4) with a mean radiologic size 7.3 cm, and some had a cystic component (n = 9). Three cell types (osteoclastic giant cells, pleomorphic tumor giant cells, and spindled/histiocytoid cells) were observed in 12 of 15 specimens (80%); and pancreatic ductal adenocarcinoma (PDAC) was present in 11 specimens. FNA diagnoses were UOC (n = 6), PDAC (n = 5), poorly differentiated carcinoma (n = 2), "suspicious for neoplasm" (n = 1), and "negative" (n = 1). Five of 5 specimens with osteoclastic giant cells were positive for cluster of differentiation 68 (CD68) (a glycoprotein that binds to low-density lipoprotein). Pleomorphic tumor giant cells and spindled/histiocytoid cells were positive for pancytokeratin (6 of 7 specimens), CAM5.2 (2 of 3 specimens), and epithelial membrane antigen (2 of 2 specimens). INI-1 protein expression was retained in 3 of 3 specimens. The Ki-67 labeling index was assessed in 3 specimens and was 12%, 18%, and 40%; 4 of 12 resected UOCs were pure, and 8 were mixed with PDAC. One resection specimen had intraductal papillary mucinous neoplasm, and 2 had mucinous cystic neoplasms. The median overall survival (OS) of patients who had UOCs identified on FNA was 8 months (6 died [OS, 8 months; range, 2-22 months], and 8 remained alive [OS, 3 months; range, 1-27 months]), which was similar to the survival of 74 patients who had PDACs identified on FNA (OS, 15 months; $P = .279$) but worse than that of the 27 patients with UOCs who did not undergo FNA (OS, 92 months; $P = .0135$). **CONCLUSIONS:** The 3 classical UOC cell types are identifiable on FNA, making cytologic diagnosis possible if considered in the differential. A PDAC component is often also observed. The survival advantage of UOC over pure PDAC appears to be negated by FNA and requires further investigation. ***Cancer Cytopathol* 2017;125:563-75**. © *2017 American Cancer Society.*

KEY WORDS: cytology; fine-needle aspiration (FNA); osteoclast-like giant cell carcinoma; pancreas; undifferentiated carcinoma with osteoclastic giant cells of the pancreas.

INTRODUCTION

The vast majority of pancreatic masses represent pancreatic ductal adenocarcinoma (PDAC), which has a dismal 5-year survival rate of less than 8% and is currently the third leading cause of cancer-related deaths in the United States.[1] Undifferentiated pancreatic carcinoma with osteoclastic giant cells (UOC) is an extremely rare pancreatic

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Received: November 4, 2016; **Revised:** January 13, 2017; **Accepted:** February 21, 2017

Published online April 3, 2017 in Wiley Online Library (wileyonlinelibrary.com)

DOI: 10.1002/cncy.21859, wileyonlinelibrary.com

cancer that has a preponderance of osteoclastic giant cells (OGCs) exhibiting all the characteristics of osteoclasts of bone. It was first described by Sommers and Meissner in 1954 as "unusual carcinoma of the pancreas."[2] In 1968, Rosai named these tumors "carcinomas of pancreas simulating giant cell tumor of bone."[3] Its true incidence remains unknown because of the plethora of names by which it has been described, including "pleomorphic carcinoma of pancreas, giant cell carcinoma," "osteoclastic giant cell tumor or carcinoma," "sarcomatoid carcinoma," and "carcinosarcoma," to name a few. In 2010, the World Health Organization classified these tumors as variants of PDAC under the heading "undifferentiated carcinoma with osteoclastic giant cells,"[4] and they have been identified as fundamentally epithelial-derived tumors with mesenchymal differentiation.[3,5]

The age of patients with UOC is 62 years, but age ranges widely from 32 to 93 years.[4,6–8] Tumors are typically large and circumscribed and are defined by nonneoplastic, phagocytic, OGCs containing over 20 bland nuclei in a background of "sarcomatoid" carcinoma, which may produce osteoid.[6,8–10] Some tumors exhibit polypoid intraductal or intra-ampullary growth or cystic degeneration,[8,11,12] whereas others arise in neoplastic mucinous cysts (mucinous cystic neoplasm [MCN] or intraductal papillary mucinous neoplasm [IPMN]).[8,13–15]

Other than the macrophage-like OGCs that are typical of this tumor,[9] 2 other distinct tumor cell types—including large, highly pleomorphic mononuclear tumor giant cells as well as small, spindled or histiocytoid tumor cells (SHCs) that sometimes resemble stromal cells—may be observed. Morphologic, immunohistochemical, molecular, and ultrastructural studies have indicated that OGCs represent benign histiocytic cells likely recruited by the tumor's sarcomatoid component.[9,16] It has been postulated that elevated chemoattractants noted in oral squamous and inflammatory breast cancers play a similar chemotactic role in some pancreatic and ampullary cancers, including UOC.[8,17,18]

OGCs express cluster of differentiation 68 (CD68) (a glycoprotein that binds to low-density lipoprotein), vimentin, and leukocyte common antigen and are negative for keratin and p53; however, the truly malignant cells in this tumor (ie, the pleomorphic tumor giant cells [TGCs] and SHCs, which are often overlooked in the background) strongly express vimentin and variably but typically express keratin, exhibit a mutant p53 staining pattern (with diffuse positivity), and have an elevated Ki-67 proliferation index.[4,8–10,19,20] UOCs frequently have an associated component of conventional PDAC.[4,8] Whereas some studies suggest an overall poor prognosis for patients with UOC, with mean survival of 12 months,[4,7] more recent studies have indicated that these tumors have a more protracted clinical course relative to conventional PDACs.[8,21–23]

Although the histologic features of UOC (aka, "osteoclastic giant cell carcinoma") are well known, its cytologic features are described only rarely and mostly in isolated reports or small series.[12,24–38] Herein, we present the cytologic findings in 15 fine-needle aspirations (FNAs) defined by the presence of OGCs and highlight useful diagnostic cytologic characteristics as well as pertinent clinicopathologic features and associations. To date, this is the largest cytologic series in the English literature.

MATERIALS AND METHODS

A multi-institutional pathology database search yielded 15 FNA specimens from 14 patients, including 6 from Emory University's archives and consultation files; 2 each from Thomas Jefferson University (Philadelphia, Pa), the University of Michigan (Ann Arbor, Mich), and the University of British Columbia (Vancouver, BC); and 1 each from Northside Hospital (Atlanta, Ga), the Mayo Clinic (Rochester, Minn), and the Cleveland Clinic (Cleveland, Ohio). Resected, pure, undifferentiated carcinoma lacking OGCs were excluded from analysis.

All patients underwent image-guided (endoscopic ultrasound [n = 11] or computerized tomography [n = 3]) FNAs, which included 1 to 7 passes per patient (mean, 3.9 passes per patient), with or without onsite evaluation. Cyst fluid analyses and molecular studies were not performed on the specimens. Cytologic material, including smears, ThinPrep, cellblocks, and immunocytochemical stains (when available), were reviewed. On average, 7 slides were available per case (range, 2-19 slides per case), including both Papanicolaou and Diff-Quik stained slides. Core biopsies were also available for review in 1 patient (case 14).

Twelve of 14 patients (86%) underwent follow-up resections, and their tumors' clinicopathologic characteristics were documented. In addition, cytologic samples were analyzed for the presence and frequency (scored as 1 [focal], 2 [moderate], or 3 [extensive]) of 4 cell types: 1) OGCs, 2) SHCs, 3) mononuclear TGCs, and 4) PDAC component. Necrosis and acute inflammation also were documented.

Comparison of Survival Differences Between Aspirated UOCs, UOCs With No Prior FNA, and Conventional PDAC With Prior FNA

The survival of patients with UOC who underwent FNA (n = 14) was contrasted with survival in a cohort that had unaspirated, resected UOC in the authors' database (n = 27), a detailed analysis of which was previously published,[8] and with survival in a cohort that had conventional PDAC and underwent FNA (n = 74).

RESULTS

Clinical Characteristics

The 15 specimens were from 14 patients, including 6 men and 8 women who ranged in age from 35 to 77 years (mean age, 65.3 years). Seven tumors were located in the pancreatic head, 3 were located in the body, and 4 were located in the tail. The clinicopathologic findings are summarized in Table 1.

Radiologic Findings

On imaging, tumors ranged in size from 2.0 to 25 cm (mean size, 9.0 cm) and were either purely cystic (n = 2; 1 was suggestive of a pseudocyst), purely solid (n = 3; with radiologic diagnoses of PDAC in 2 and sarcoma in 1), or mixed cystic and solid masses (n = 9). Other radiologic diagnoses included IPMN and cystic pancreatic neuroendocrine tumor (PanNET), among others (Table 1). It is noteworthy that only 1 tumor, a 9.0-cm solid pancreatic mass, was called sarcoma on imaging.

Cytologic Findings

Diff-Quik, Papanicolaou smears, and ThinPrep slides ranged from moderately cellular (14 of 15 cases; 93%) to hypocellular (1 of 15 cases; 7%). There were 3 distinct types of tumor cells: 1) multinucleated OGCs, 2) large TGCs, and 3) smaller SHCs (Figs. 1-5). Malignant TGCs and SHCs were observed in clusters, syncytial groups, and singly dispersed and had high nuclear-to-cytoplasmic ratios and nuclear irregularity (both were present in 12 of 15 specimens; 80%) (Figs. 1-5). In addition, various multinucleated osteoclast-like giant cells, ranging in size from 50 to 500 microns, were observed in 12 of 15 FNAs (80%) (Figs. 1 and 2). Of the 3 FNAs that lacked all 3 cell types, 1 represented a 25-cm MCN with a 2.0-cm UOC focus that was likely not sampled by FNA; another (case 15) was almost exclusively PDAC with only scattered, small patches of UOC component (overall estimated size, <0.5 cm) identified only on the resection specimen; and the third FNA (case 6) had acellular smears, with rare, atypical glandular cells on cell block but was called "negative" on initial cytologic diagnosis. Mitotic figures were identified in rare tumor nuclei (Fig. 3). Background necrotic debris (12 of 15 specimens; 80%) and a neutrophilic inflammatory infiltrate (6 of 15 specimens; 40%) were observed in several FNAs (Fig. 2).

On Papanicolaou-stained slides (smears and ThinPrep slides), cell blocks, and cores, the OGCs were easily identifiable, with multiple (≥10), centrally clustered, oval or raisinoid nuclei; indistinct nucleoli; and abundant, pale blue-gray or eosinophilic cytoplasm (Figs. 1 and 2). SHCs ranged from long, slender, and atypical to round and bland (Fig. 1). Pleomorphic tumor cells had large, bizarre hyperchromatic to hypochromatic nuclei and were single-lobed or polylobated, some with mummified features, and macronucleoli (Figs. 1 and 3). In all cases, TGCs were the most frequent, followed by SHCs, then OGCs.

An adenocarcinoma component was noted on smears in 11 of 15 specimens (73%). This was represented by sheets, clusters, or singly dispersed malignant epithelial cells, with or without cytoplasmic mucin vacuoles or overt gland formation (Fig. 4). The corresponding resection specimens in these 11 patients also had a PDAC component.

Cell blocks were available for review in 13 of 15 specimens (87%) and were very helpful in supporting the diagnosis, because they often revealed OGCs (Figs. 1 and 2). Single-cell necrosis and confluent necrosis were present in 12 of 15 specimens (80%). A core biopsy also was available for case 14 and exhibited the 3 classical cell types of UOC (Fig. 5). The cytologic findings are summarized in Table 2.

The final diagnoses in associated cytopathology reports were UOC (6 of 15 specimens; 40%), poorly differentiated carcinoma (2 of 15 specimens; 13%), "suspicious for neoplasm" (1 of 15 specimens; 7%), "negative for malignant cells"(1 of 15 specimens; 7%), and PDAC (5 of 15 specimens; 33%), 1 of which (case 7) arose in a neoplastic mucinous cyst that exhibited mucinous epithelium on FNA with high-grade atypia and necrosis. It is noteworthy that, on re-review, the "negative" FNA (case 6) in hindsight would best have been interpreted as "atypical cells present or suspicious for adenocarcinoma," because the cell block revealed a single, highly atypical gland, whereas the smears were mostly acellular.

TABLE 1. Clinicopathologic Characteristics of Undifferentiated Pancreatic Carcinoma With Osteoclastic Giant Cells (n = 15)

FNA No.	Age, y	Sex	Location	Imaging Modality	Size on Imaging, cm	Additional Radiologic Findings	Radiologic Diagnosis	Cytologic Diagnosis	Histologic Diagnosis	Size of Invasion, cm	Follow-Up Status
1[a]	71	Woman	Head	MRI	7.2	Clustered cysts w/septal enhancement; no large solid component	IPMN	Poorly differentiated carcinoma	Mixed UOC and PDAC	3.0	10 mo; LTF/U after chemo
2[a]								Poorly differentiated carcinoma			
3	54	Woman	Body	N/A	N/A	N/A	N/A	UOC	UOC	2.1	2.2 mo; alive, NED
4	66	Woman	Tail	MRI	6.8	Solid and cystic mass	PDAC	UOC	Mixed UOC and PDAC	7.1	10.2 mo; dead w/liver mets (PDAC component)
5	51	Woman	Head	CT	3.4	Cystic mass w/peripheral nodular components	Cystic NET	Suspicious for neoplasm	Mixed UOC and PDAC	5.4	4.1 mo; alive, NED, received radiation
6	75	Woman	Head	MRI	N/A	Pancreatic neck stricture, severe pancreatic duct dilatation; no measurable mass	Chronic pancreatitis vs tumor	Negative for malignant cells	Mixed UOC and PDAC	0.6	12.9 mo; dead
7	35	Woman	Tail	MRI	25.0	Complex solid and cystic mass	PDAC	PDAC possibly arising in NMC	Mixed UOC and PDAC, MCN w/HGD	2.5	27 mo; alive, NED
8	49	Woman	Tail	MRI	5.6	Cystic and solid mass	Possible cystic NET	PDAC	UOC, PDAC and MCN	1.0	1.2 mo; alive w/UOC liver mets
9	43	Man	Head	CT	6.0	Cystic lesion	Pseudocyst	UOC	UOC	6.5	21.18 mo; dead
10	77	Woman	Head	CT	9.0	Solid mass	Sarcoma	UOC	N/A	N/A	1.7 mo; dead
11	65	Man	Head	EUS	2.0	Solid mass	PDAC vs lymphoma	PDAC	UOC and PDAC	2.5	6.13 mo; dead
12	67	Man	Tail	EUS	4.9	Solid and cystic body and tail mass	PDAC	UOC	UOC and IPMN w/HGD	11.0	3.17 mo; alive
13	59	Man	Head	EUS	2.2	Mass in head	PDAC	PDAC	UOC and PDAC	4.1	5.1 mo; dead w/liver mets
14	65	Man	Body	MRI	13.0	Solid and cystic mass in body	PDAC	UOC	N/A	N/A	3.15 mo; alive w/liver mets
15	75	Man	Body	EUS	5.4	Solid mass with 1.3 cm cyst	PDAC	PDAC	UOC and PDAC	7.3	22 mo; alive, NED postchemo

Abbreviations: Chemo, chemotherapy; CT, computerized tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; LTF/U, lost to follow-up; MCN, mucinous cystic neoplasm; Mets, metastasis; MRI, magnetic resonance imaging; N/A, not available; NED, no evidence of disease; NET, neuroendocrine tumor; NMC, neoplastic mucinous cyst; PDAC, pancreatic ductal adenocarcinoma; UOC, undifferentiated pancreatic carcinoma with osteoclastic giant cells.

[a] Cases 1 and 2 were specimens from the same patient.

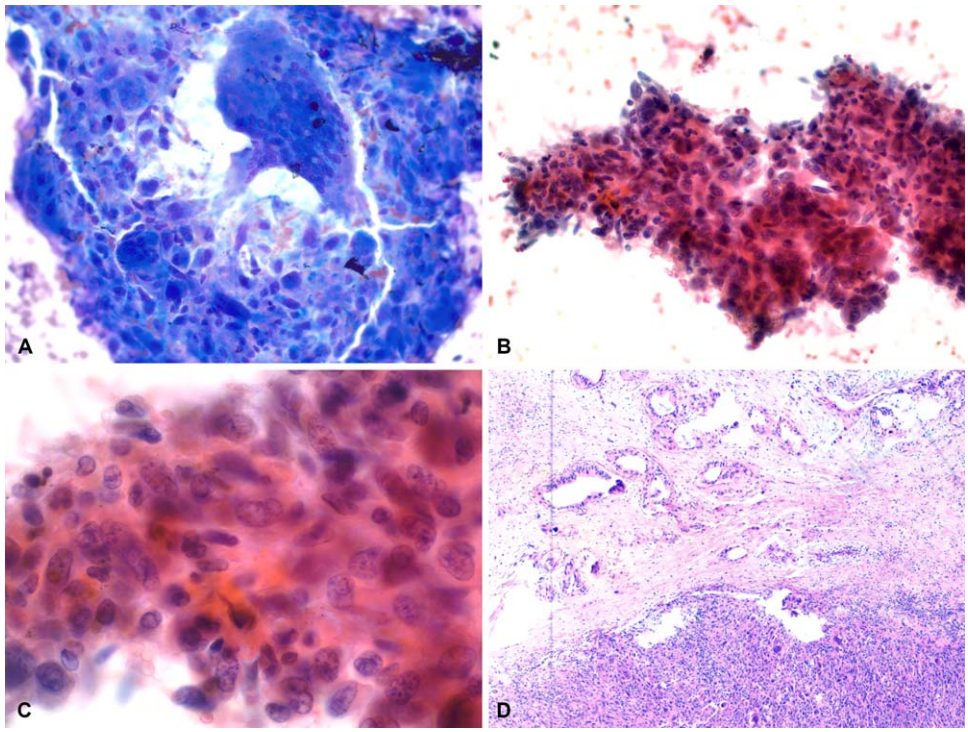

Figure 1. In case 4, (A) a hypercellular smear is composed of 3 distinct cell types, including a centrally located, multinucleated osteoclastic giant cell surrounded by pleomorphic tumor giant cells and spindled and histiocytoid tumor cells (Diff-Quik stain, original magnification ×200). (B) Tumor cells in a syncytial cluster include pleomorphic tumor giant cells and spindled cells with a multinucleated osteoclastic giant cell on the right (Papanicolaou stain, original magnification ×200). (C) Tumor giant cells are markedly pleomorphic, with nuclear irregularity and hypochromasia (Papanicolaou stain, original magnification ×400). (D) A corresponding resection sample from the same patient exhibits a mixed conventional pancreatic ductal adenocarcinoma (upper one-half) and a circumscribed, undifferentiated carcinoma with osteoclastic giant cells (lower one-half; H&E stain, original magnification ×40).

Immunocytochemical Findings

Immunocytochemical stains were performed on several specimens and revealed the following pertinent results: CD68 (a histiocytic marker) was diffusely and strongly positive in OGCs (5 of 5 specimens) and was focally positive in rare, isolated histiocytoid cells. Epithelial markers were frequently positive, albeit focally, in TGCs and SHCs; pancytokeratin was positive in 6 of 7 specimens tested and was stronger in tumor giant cells; anticytokeratin (CAM 5.2) and epithelial membrane antigen (EMA) were focally positive in TGCs (2 of 3 specimens) and SHCs (2 of 2 specimens); 1 specimens had a mutant p53 pattern (diffuse, strong positivity), whereas p53 was negative in 2 specimens (Fig. 5). Expression of INI-1 protein, which has recently been identified as a marker of a specific subset of undifferentiated pancreatic carcinoma (typically without OGCs),[39] was retained in all 3 tested tumors. Additional, pertinent, negative stains include S100 in 3 of 3 specimens. It is noteworthy that Ki-67 immunostaining was performed in 3 tumors, and the proliferation index was 12%, 18%, and 40%, respectively.

Histologic Findings in the 12 Resected Cases

Tumors were located in the pancreatic head (n = 6), body (n = 2), and tail (n = 4), and resection specimens included 6 pancreatoduodenectomies and 6 distal pancreatectomies. Two tumors were not resected. Tumors ranged in size from 0.6 to 13.0 cm (mean size, 6.9 cm) and were mostly demarcated and solid, with a cystic component in 11 cases; 3 of 11 cystic tumors had associated neoplastic mucinous cysts (IPMN with high-grade dysplasia [n = 1] and MCN with high-grade dysplasia [n = 2]). Of the 12 resection specimens, 4 (33%) were pure UOC, and 8 (67%) had admixed PDAC, ranging from focal (10% in 5 specimens) to extensive (30%-90% in 3 specimens) (Fig. 1). One unresected tumor was a pure UOC on FNA and core biopsy, whereas the other was "mixed." The 12 resection specimens had lymph node sampling (range, 15-33

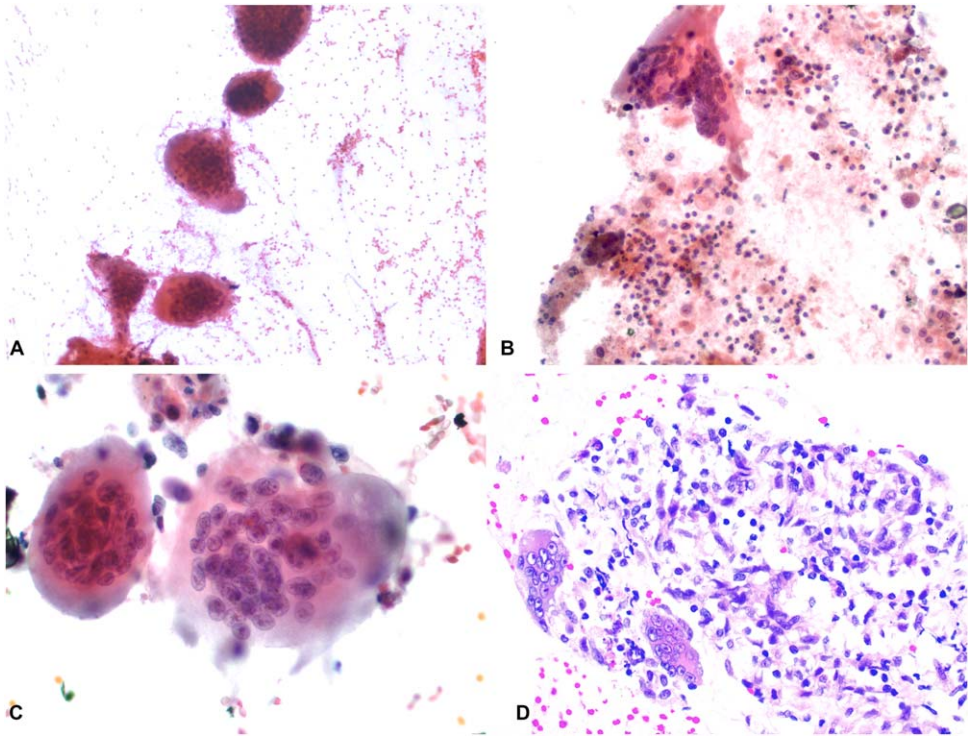

Figure 2. The morphologic spectrum of osteoclastic giant cells is illustrated. (A) Numerous multinucleated giant cells ranging in size from 50 to 500 microns are present in this example (Papanicolaou stain, original magnification ×100). (B) Osteoclastic giant cells are noted in a background of necrotic debris, neutrophils, and rare pleomorphic tumor giant cells (Papanicolaou stain, original magnification ×200). (C) Osteoclastic giant cells have centrally clustered, bland nuclei with fine chromatin (Papanicolaou stain, original magnification ×400). (D) In this example (case 11), osteoclastic giant cells were infrequent and were best visualized on cell block, in which they had more atypical nuclei with washed out chromatin and large, prominent nucleoli admixed with spindled tumor cells (H&E stain, original magnification ×400).

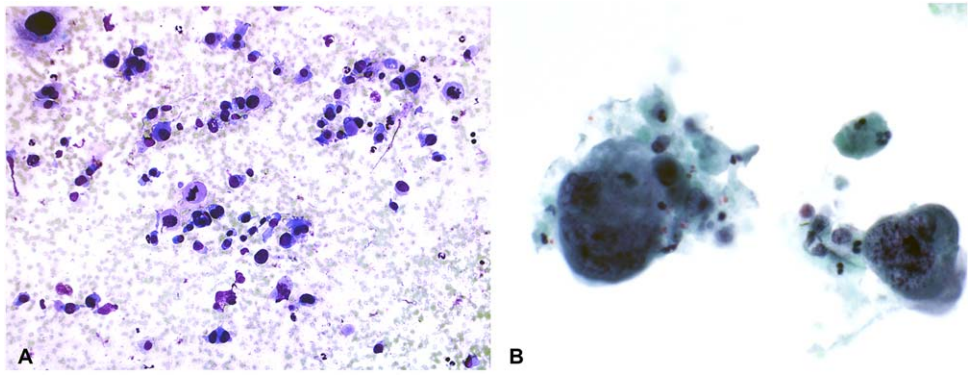

Figure 3. The morphologic spectrum of pleomorphic tumor giant cells is illustrated. (A) Numerous, singly dispersed epithelioid tumor cells with high nuclear-to-cytoplasmic ratio, irregular nuclei, and numerous abnormal mitotic figures are observed in case 3 (Diff-Quik stain, original magnification ×200). (B) On a ThinPrep smear, these pleomorphic tumor giant cells (case 1) have a high nuclear-to-cytoplasmic ratio with coarse chromatin and marked nuclear irregularity (Papanicolaou stain, original magnification ×400).

lymph nodes), and 4 patients had lymph node metastasis. One patient (case 8) had liver metastasis at the time of pancreatectomy. Lymphovascular and perineural invasion were observed in 5 (42%) and 6 (50%) resection specimens, respectively, and tumor margins were positive in 1 of 12 (8%). Regarding pathologic(p) TNM classification

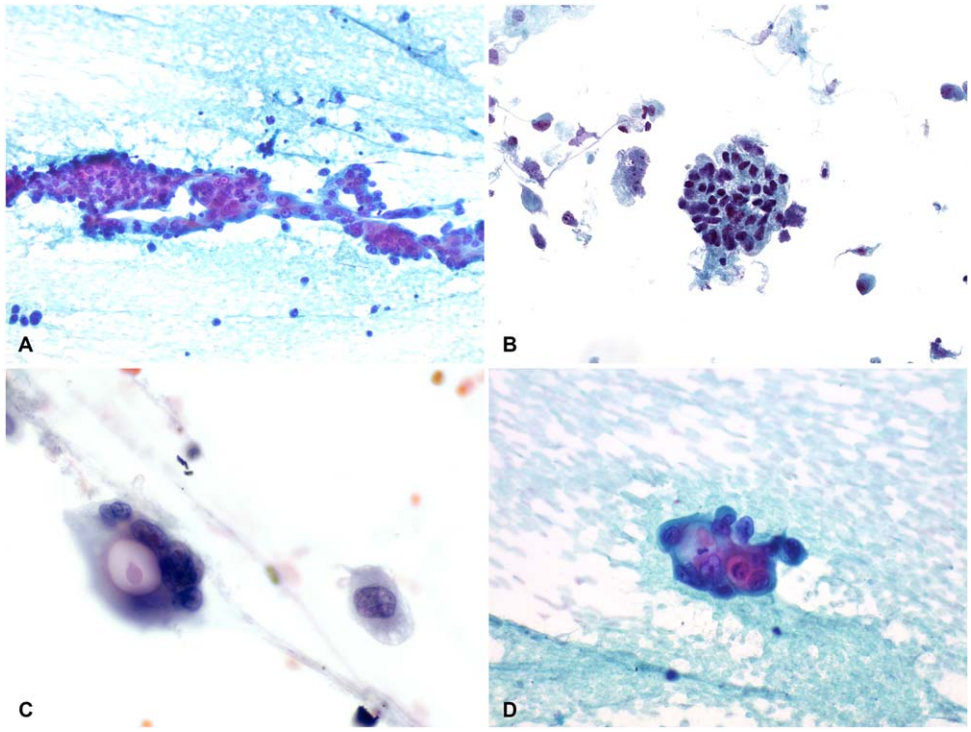

Figure 4. The morphologic spectrum of pancreatic ductal adenocarcinoma component is illustrated. (A) In this example (case 11), a sheet of malignant ductal cells with nuclear hypochromasia and prominent nucleoli is observed with background pleomorphic tumor giant cells (Papanicolaou stain, original magnification ×200). (B) A ThinPrep smear (case 13) exhibits a cluster of slightly pleomorphic ductal cells with high nuclear-to-cytoplasmic ratio and mild pleomorphism in a background of necrosis and rare, single, pleomorphic tumor giant cells (Papanicolaou stain, original magnification ×200). (C) In this example (case 4), the adenocarcinoma component was more difficult to identify and was present as rare, isolated clusters of epithelial cells with prominent cytoplasmic vacuoles containing targetoid mucin droplets (Papanicolaou stain, original magnification ×400). (D) This cell cluster from case 11 is recognizable as adenocarcinoma because of the central mucin vacuole (Papanicolaou stain, original magnification ×400).

(according to the American Joint Committee on Cancer *Cancer Staging Manual* seventh edition),[40] 1 tumor (8%) was pT1N0MX, 4 (33%) were pT2N0MX, 5 (42%) were pT3N0MX, 1 (8%) was pT3N1MX, and 1 (8%) was pT3N1M1. One unresected tumor was staged as T3N1M1 (case 14) based on markedly enlarged peripancreatic lymph nodes and a large liver mass on imaging.

Follow-Up Information

At an overall median follow-up of 5 months (range, 1-27 months), 1 patient died of perioperative complications, 8 were alive (6 with no evidence of disease and 2 with liver metastasis; median survival, 3 months; range, 1-27 months), 6 were dead of disease (range, 1-21 months), and 1 was lost to follow-up at 3 months (Table 3). Chemotherapy was received by 5 patients (survival, 1-27 months), including 3 who were alive at last follow-up, 1 who had died (survival, 10 months), and 1 who was lost to follow-up after chemotherapy (for survival details on each patient, see Table 1).

Comparison of Survival Between Aspirated UOCs, UOCs Without Prior FNA, and Conventional PDACs With Prior FNA

When the patients with UOC who underwent FNA (n = 14) were compared with a cohort of patients who had UOCs that were not previously aspirated (but not stage matched; n = 27), there was a statistically significant difference in survival between them, with a significantly shorter median overall survival observed in the UOC FNA patients (8 vs 92.4 months; $P = .0135$) compared with those who had UOC but did not undergo aspiration before resection (Table 3, Fig. 6). When the same UOC FNA group (n = 14) was compared with a conventional PDAC FNA cohort (also not stage matched; n = 74), the UOC FNA cohort continued to trend toward shorter overall survival compared with the PDAC FNA cohort

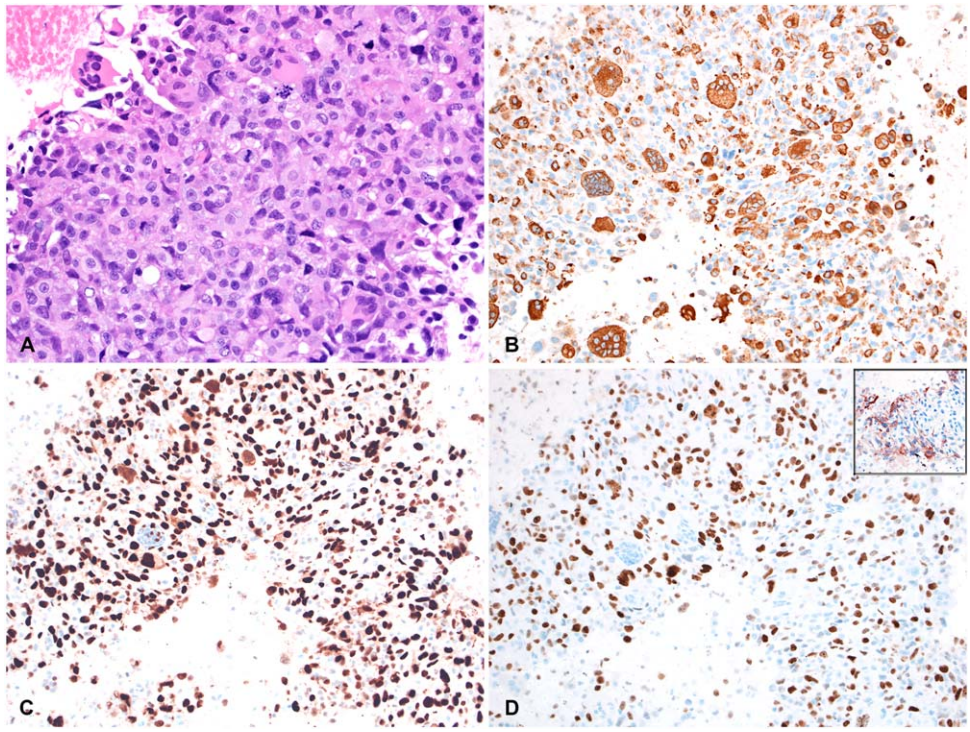

Figure 5. In case 14, a core biopsy reveals (A) sheets of pleomorphic tumor giant cells, histiocytoid tumor cells, and osteoclastic giant cells (H&E stain, original magnification ×400); (B) osteoclastic giant cells and scattered histiocytoid tumor cells that were strongly positive for CD68 original magnification ×200); and strong, diffuse positivity for (C) p53 and (D) and Ki-67 is observed in pleomorphic and histiocytoid tumor cells but is negative in osteoclastic giant cells . Tumor giant cells and scattered spindled/histiocytoid cells are focally positive for pancytokeratin (D, inset). (original magnification ×200).

TABLE 2. Cytologic Findings in Undifferentiated Pancreatic Carcinoma With Osteoclastic Giant Cells (n = 15)

Case No.	Cytologic Diagnosis	OGCs[a]	TGCs[a]	SHCs[a]	PDAC Component[a]	Neutrophils[a]	Necrosis
1	PDCA	1	3	1	1	2	Yes
2	PDCA	1	3	1	1	2	Yes
3	UOC	2	3	3	0	2	Yes
4	UOC	3	3	3	1	2	Yes
5	Suspicious for neoplasm	2	2	1	2	2	Yes
6	Negative	0	0	0	1	0	No
7	PDAC possibly arising in NMC	0	0	0	1	0	Yes
8	PDAC	1	3	3	1	0	Yes
9	UOC	2	2	1	0	0	No
10	UOC	1	1	3	2	0	No
11	PDAC	2	1	2	3	0	Yes
12	UOC	3	3	3	0	0	Yes
13	PDAC	3	3	2	1	0	Yes
14	UOC	3	3	3	0	0	Yes
15	PDAC	0	0	0	3	0	Yes
Total, n = 15		12/15 (80%)	12/15 (80%)	12/15 (80%)	11/15 (73%)	5/15 (33%)	Yes: 12/15 (80%)
Frequency, n = 45		24/45 (56%)	30/45 (67%)	26/45 (57%)	17/45 (38%)	10/45 (22%)	—

Abbreviations: PDCA, poorly differentiated carcinoma; PDAC, pancreatic ductal adenocarcinoma; OGCs, osteoclastic giant cells; SHCs, spindled/histiocytoid cells; TGCs, pleomorphic tumor giant cells; UOC, undifferentiated pancreatic carcinoma with osteoclastic giant cells.
[a] 0 Indicates absent; 1, present focally; 2, moderate amount; 3, extensive.

TABLE 3. Overall Patient Survival Based on Diagnosis and History of Previous Fine-Needle Aspiration

Variable	UOC With Prior FNA (n = 14)	UOC Without Prior FNA (n = 27)	PDAC With Prior FNA (n = 74)	*P*
Median survival, mo	8	92.4	15.6	.0578
Survival, %				
1 Year	39.3	87.4	60.7	
3 Years	—	57.5	31.6	
5 Years	—	57.5	23	

Abbreviations: FNA, fine-needle aspiration; PDAC, pancreatic ductal adenocarcinoma; UOC, undifferentiated pancreatic carcinoma with osteoclastic giant cells.

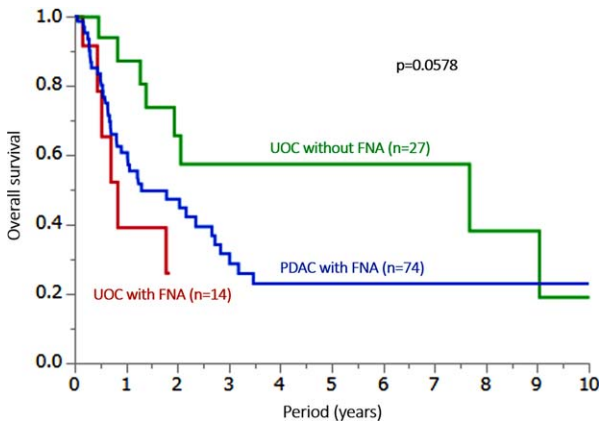

Figure 6. Kaplan Meier survival curves indicate that patients with previously aspirated undifferentiated pancreatic carcinoma with osteoclastic giant cells (UOC) had significantly shorter survival than their nonaspirated counterparts (8 vs 92 months; $P = .0135$) and had comparable if not worse survival than patients who had aspirated conventional pancreatic ductal adenocarcinomas (PDACs) (8 vs 15 months; $P = .2791$). This is in contrast to patients with nonaspirated UOCs, who had a longer survival (92 vs 15 months; $P = .058$) than those with aspirated PDACs. FNA indicates fine-needle aspiration.

(median survival, 8 vs 15 months), but the difference failed to reach statistical significance ($P = .279$). In addition, a more striking survival advantage for the UOC non-FNA group (n = 27) was observed compared with the 74 patients in the PDAC FNA group, but this difference also fell short of statistical significance ($P = .058$).

DISCUSSION

The unique cytologic features of UOCs include a mixture of large, bland, multinucleated, OGCs as well as highly pleomorphic malignant TGCs and small SHCs. These are often present in a background of necrosis and variable neutrophilia, and they may be associated with a conventional PDAC component, which is a frequent finding on FNA of UOCs.[34]

The 3 classical cell types of UOC are identifiable on FNA in the majority of cases, making cytologic distinction possible if this entity is considered in the differential. This was not just evident in our cohort but also was reported by others.[31,34,37,38] UOC is recognizable not only on FNA but also on brushings of its intraductal counterpart.[12] The OGCs are perhaps easiest to recognize and, once identified, should prompt a search for the other 2 cell types. It is noteworthy that, although only 40% of cases were correctly called UOC on cytology, a review of the original cytology material from the remaining cases revealed that 60% of the cases initially called PDAC, including both "poorly differentiated carcinomas" and the "suspicious for neoplasm" case, all had the 3 distinct tumor cell types typical of UOC, particularly OGCs. Thus, 80% of specimens could have been accurately identified as having a UOC component on FNA. Only 3 specimens lacked all 3 cell types on FNA. One had features of a neoplastic mucinous cyst with high-grade atypia and was diagnosed on cytology as "(at least) adenocarcinoma in situ arising in a neoplastic mucinous cyst with high-grade atypia; suspicious for invasion." On resection, this turned out to be a 25-cm MCN with extensive high-grade dysplasia and a 2-cm focus of mixed UOC and PDAC, which was unlikely to have been sampled during FNA. Despite generous sampling in 1 case, only PDAC was identified on FNA, whereas the corresponding resection revealed 90% PDAC and a very limited UOC component.

In mixed cases, the UOC component may be focal, emphasizing the importance of careful cytologic examination and histologic sampling. In addition, for those with an extensive cystic component (whether because of degeneration or concomitant neoplastic mucinous cyst), the UOC component may be overlooked. Tumors may also exhibit extensive fibrosis, hemorrhage, and even osteoid formation, which can lead to nondiagnostic samples.

Tumors are known by names such as "osteoclastic giant cell tumor of the pancreas" and "pleomorphic (giant cell) carcinomas of the pancreas."[34,36] Some have suggested differences in behavior based on the amount of OGCs, with less aggressive behavior in tumors more rich in OGCs. It is important to note that all UOCs have similar behavior despite quantities of the 3 distinct cell types, including OGCs.

The significance of a UOC component cannot be overstated; in a recent histologic study of 38 UOCs, we demonstrated that (whether pure or combined with PDAC) patients who have tumors with a UOC component have a more protracted clinical course with significantly longer 5-year survival than those with conventional PDAC (59.1% vs 15.7% in poorly differentiated PDACs).[8] This suggests that UOCs should be resected once identified if patients are good surgical candidates. However, an interesting observation in our limited FNA cohort was the shorter survival of patients with UOC who underwent FNA, which was very similar to if not worse than that of patients with PDACs, whereas patients who had UOCs without undergoing FNA before resection had a much better prognosis than patients in both of the other groups. This may be attributable to selection bias, in which patients with more aggressive UOCs were more likely to undergo diagnostic procedures perhaps because of symptoms. In addition, patients in the PDAC and nonaspirated UOC cohorts were not stage-matched with our FNA cohort, which may also account for survival differences. Nevertheless, in the current study, the shorter survival of our patients with UOC who underwent FNA, relative to our previously studied UOC group, raises concern regarding whether FNA has a negative impact on the prognosis for these patients. The FNA procedure is safe for the majority of neoplasms, including pancreatic tumors. In fact, we recently analyzed our PDAC database, comparing aspirated PDACs of the pancreatic tail with those that had not been aspirated before resection and observed identical survival in both groups (unpublished data). However, it is possible that some tumors (pancreatic colloid carcinomas and mixed salivary gland tumors) may spread after manipulation and may require removal of the needle tract, similar to mixed salivary glands tumors.[41,42] If this observation is ultimately confirmed by other studies, then UOC may prove to be 1 of those rare tumors with unique biologic properties that create vulnerability to iatrogenic spread.

The clinicopathologic characteristics in our cohort are similar to previous reports, in that our patients were predominantly women, with a mean age of 65 years,[4,6,7,10] with large tumors (mean size, 6.9 cm), many with a PDAC component and tumoral intraepithelial neoplasms (MCN and IPMN) in 20%.[8,13] The coexistence of UOC with MCN and IPMN is well documented.[8,13–15] A cystic component (mostly cystic degeneration) was identified in most UOCs in our cohort. This can cause radiologic misdiagnosis as a neoplastic mucinous cyst or pseudocyst, or it may limit sampling of the tumor's solid component. Knowledge of the association between UOC and neoplastic mucinous cysts is critical in ensuring that resected mucinous cysts are extensively sampled so that a UOC component is not missed. UOCs may also protrude as polyps into the pancreatic duct or bile duct, duodenum, or ampulla, leading to radiologic misdiagnosis as IPMN, intra-ampullary tubulopapillary neoplasm, or intraductal papillary neoplasm of bile duct.[8,11,12]

Immunohistochemistry can be especially helpful in the cytohistologic diagnosis of UOC, because OGCs consistently express the histiocytic marker CD68 and are typically negative for epithelial markers and Ki-67.[8,9] In addition, malignant pleomorphic tumor cells and SHCs variably express pancytokeratin, CAM5.2, and EMA, which are typically negative in OGCs. The Ki-67 proliferation index is also high in these cells, and p53 may be expressed by malignant TGCs and SHCs but is negative in OGCs.[4,8] Only 1 of 4 UOCs in our cohort had a mutant p53 staining pattern.

The significance of the presence and amount of PDAC in these tumors has been previously studied, including by our group.[8] In our prior study we identified a PDAC component in 75% of cases; however, when PDAC percentages were examined, they had no effect on overall survival.

Differential Diagnosis

Multinucleated (reactive or neoplastic) giant cells can be observed in benign and malignant processes in the pancreas, including chronic pancreatitis, PanNET, and solid-pseudopapillary neoplasm (SPN).[35,43,44] The highly atypical, hyperchromatic multinucleated giant cells in PanNETs represent neuroendocrine "atypia" of a symplastic nature, a well known degenerative phenomenon with no clinical significance.[44] Degenerating "cercariform" giant cells have also been described in SPN.[43] In both PanNETs and

SPNs, background tumor cells exhibit the other cytologic characteristics that typify these neoplasms (such as plasmacytoid cells with salt-and-pepper chromatin in PanNETs and open chromatin and longitudinal nuclear grooves in SPNs), facilitating their distinction.

A major differential of UOC is undifferentiated PDAC, not otherwise specified. On cytology, these tumors are highly pleomorphic with clustered or singly dispersed, highly malignant cells with or without cytoplasmic mucin vacuoles but with high nuclear-to-cytoplasmic ratios, necrosis, and brisk mitotic activity. However, these tumors lack OGCs, which distinguishes them from UOC. In addition, tumor cells in undifferentiated PDAC are keratin-positive and do not express histiocytic markers. Their prognosis, however, is typically much worse than that for UOC.

Another "undifferentiated" pancreatic primary tumor, undifferentiated rhabdoid carcinoma, with v-Ki-ras2 Kirstin rat sarcoma viral oncogene homolog (*KRAS*) alterations and SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1 (SMARCB1) (INI-1) loss is an important differential, as recently described by Agaimy et al.[39] This tumor typically exhibits eosinophilic rhabdoid cells with pleomorphic nuclei and prominent nucleoli, which may mimic the TGCs of UOC. However, they exhibit either loss of INI-1 or *KRAS* mutations, unlike UOC, which to date has not demonstrated INI-1 loss. Undifferentiated rhabdoid pancreatic carcinomas do not contain OGCs.[39] We performed INI-1 testing in 3 UOCs, and it was retained in all 3.

Malignant melanoma frequently metastasizes to the pancreas and may be confused with UOC.[45,46] Melanoma tumor cells may be spindled or epithelioid and single, with prominent nucleoli that mimic UOC. In addition, multinucleated tumor giant cells may be confused with the OGCs of UOC. However, melanoma is negative for histiocytic and epithelial markers and positive for melanoma markers S100, melan-A, and HMB-45 (homatropine methylbromide 45), which would be negative in UOC.

Although primary pancreatic sarcoma is uncommon, sarcoma metastasizing to pancreas (including leiomyosarcoma and rhabdomyosarcoma) is a known phenomenon.[45–47] Such tumors are unlikely to exhibit the bland OGCs of UOC, are typically more cellular and mitotically active than UOC, and are negative or only focally positive for epithelial markers.

Another key differential is chronic pancreatitis with exuberant granulation tissue formation. When 1 of our specimens (case 3; a consult from an outside institution) was initially reviewed by 5 experienced pathologists at our intradepartmental conference, it was interpreted as chronic pancreatitis with exuberant granulation tissue formation, because it contained numerous, foamy looking histiocytoid cells, giant cells, and capillaries. Immunohistochemical stains had been performed by the submitting institution, including pancytokeratin, CAM5.2, vascular markers (ets-related gene [ERG] and CD31), S100, CD45, anaplastic lymphoma kinase (ALK), and CD35, and all were negative. Despite strong CD68 and CD163 positivity in the OGCs, a definitive diagnosis was not reached at the outside institution. EMA testing was performed at our institution, and positive results in the SHCs were helpful in leading to an accurate cytologic diagnosis of UOC. In addition, the Ki-67 index was high in malignant cells.

Conclusion

UOC is a rare, distinctive, malignant pancreatic tumor that is typically large, frequently has a PDAC component, and has 3 classical cell types (OGCs, TGCs, and SHCs), which make cytologic diagnosis possible in the majority of cases. Tumors exhibit a strong association with mucinous tumoral intraepithelial neoplasms and have a propensity for cystic degeneration. Although it was recently demonstrated that patients with UOCs have a better prognosis than was previously believed, the prognosis in our small cohort was poor, raising the possibility of selection bias in subjecting those with more aggressive UOCs to FNA versus a negative link between FNA and survival. Larger studies are needed to explore this association.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Michelle D. Reid: Conceptualization, methodology, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, supervision, and project administration. **Takashi Muraki:** Formal analysis, investigation, resources, and writing–review and editing. **Kim HooKim:** Investigation, resources, and writing–review and editing. **Bahar Memis:** Conceptualization, methodology, formal analysis, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, supervision, and project administration. **Rondell P. Graham:** Investigation, resources, and writing–review

and editing. **Daniela Allende:** Validation, formal analysis, investigation, resources, data curation, writing–review and editing, visualization, supervision, and project administration. **Jiaqi Shi:** Resources, writing–review and editing, and visualization. **David F. Schaeffer:** Conceptualization and writing–review and editing. **Remmi Singh:** Resources. **Olca Basturk:** Conceptualization, investigation, resources, and writing–review and editing. **Volkan Adsay:** Conceptualization, methodology, formal analysis, data curation, writing–review and editing, project administration, and funding acquisition.

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