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Out of Sight, Not Out of Mind

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This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

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A 73-year-old man presented to clinic with 6 weeks of headache. He occasionally experienced generalized headaches throughout his life that resolved with naproxen. His new headache was characterized by a progressively worsening sensation of left-eye pressure with radiation to the left temple. Over the previous week, he had intermittent diplopia, left ptosis, and left lacrimation. He denied head trauma, fever, vision loss, photophobia, dysphagia, dysarthria, nausea, vomiting, or jaw claudication.

Primary headaches include tension type, migraine, and trigeminal autonomic cephalalgias (eg, cluster headache). A new headache in an older patient, particularly if protracted and progressive, prioritizes consideration of a secondary headache, which may reflect pathology within the brain parenchyma (eg, intracranial mass), blood vessels (eg, giant cell arteritis), meninges (eg, meningitis), or ventricles (eg, intraventricular cyst). Eye pain may arise from ocular and extraocular disease. Corneal abrasions, infectious keratitis, scleritis, uveitis, or acute angle-closure glaucoma are painful, although the latter is less likely given the prolonged duration of symptoms. Thyroid eye disease or other infiltrative disorders of the orbit can also cause eye discomfort.

Ptosis commonly results from degeneration of the levator aponeurosis. Other causes include third cranial nerve palsy and myasthenia gravis. Interruption of sympathetic innervation of the eyelid by lesions in the brain stem, spinal cord, lung (eg, Pancoast tumor), or cavernous sinus also can result in ptosis.

Whether the patient has monocular or binocular diplopia is uncertain. Monocular diplopia persists with only one eye open and can arise from uncorrected refractive error, corneal irregularities, lenticular opacities, or unilateral macular disease. Binocular diplopia develops from ocular misalignment due to neuromuscular weakness, extraocular muscle entrapment, or an orbital mass displacing the globe. An orbital mass would also explain the unilateral headache and unilateral ptosis.



His medical history included coronary artery disease, seronegative rheumatoid arthritis, osteoporosis, benign prostatic hypertrophy, and ureteral strictures from chronic nephrolithiasis. Following a cholecystectomy for gallstone pancreatitis 13 years earlier, he was hospitalized five more times for pancreatitis. The last episode was 6 years prior to this presentation. At that time, magnetic resonance cholangiopancreatography (MRCP) did not reveal pancreatic divisum, annular pancreas, biliary strictures, or a pancreatic mass. Esophagogastroduodenoscopy performed during the same hospitalization showed mild gastritis. His recurrent pancreatitis was deemed idiopathic.

His medications were folic acid, cholecalciferol, lisinopril, metoprolol, omeprazole, simvastatin, aspirin, and weekly methotrexate. His sister had breast and ovarian cancer, and his brother had gastric cancer. He had two subcentimeter tubular adenomas removed during a screening colonoscopy 3 years prior. He had a 30 pack-year smoking history and quit 28 years earlier. He did not use alcohol or drugs. He was a retired chemical plant worker.

Cholelithiasis (as discrete stones or biliary sludge) can trigger pancreatitis despite a cholecystectomy, but the recurrent episodes and negative MRCP should prompt consideration of other causes, such as alcohol. Hypercalcemia, hypertriglyceridemia, and medications are infrequent causes of pancreatic inflammation. IgG4-related disease (IgG4-RD) causes autoimmune pancreatitis and can infiltrate the eyelids, lacrimal glands, extraocular muscles, or orbital connective tissue. Malignancy of the pancreas or ampulla can trigger pancreatitis by causing pancreatic duct obstruction but would not go undetected for 13 years.



The patient was evaluated by an ophthalmologist and a neurologist. His heart rate was 52 beats per minute and blood pressure, 174/70 mm Hg; other vital signs were normal. He had conjunctival chemosis, ptosis, and nonpulsatile proptosis of the left eye with tenderness and increased resistance to retropulsion compared to the right eye (Figure 1). Visual acuity was 20/25 for the right eye and hand motions only in the left eye. The pupils were reactive and symmetric without afferent pupillary defect. There was no optic nerve swelling or pallor. Abduction, adduction,

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FIG 1. Image of Left Eye. The left eye exhibited conjunctival chemosis, ptosis, and proptosis with increased resistance to retropulsion.

and elevation of the left eye were restricted and associated with diplopia. Movement of the right eye was unrestricted. There was no other facial asymmetry. Facial sensation was normal. Corneal reflexes were intact. Shoulder shrug strength was equal and symmetric. Tongue protrusion was midline. Olfaction and hearing were not assessed. Strength, sensation, and deep tendon reflexes were normal in all extremities. The plantar response was flexor bilaterally.

Unilateral ptosis, chemosis, proptosis, ophthalmoplegia, eye tenderness, and visual loss collectively point to a space-occupying orbital disease. Orbital masses are caused by cancers, infections such as mucormycosis (usually in an immunocompromised host), and inflammatory disorders such as thyroid orbitopathy, sarcoidosis, IgG4-related orbitopathy, granulomatosis with polyangiitis, and orbital pseudotumor (idiopathic inflammation of the orbit). Chemosis reflects edema of the conjunctiva, which can arise from direct conjunctival injury (eg, allergy, infection, or trauma), interruption of the venous drainage of the conjunctiva by vascular disorders (eg, cavernous sinus thrombosis or carotid-cavernous fistula), or space-occupying diseases of the orbit. Monocular visual loss arises from a prechiasmal lesion, and acute monocular visual loss is more commonly caused by posterior ocular pathology (eg, retina or optic nerve) than anterior disease (eg, keratitis). Visual loss in the presence of an orbital process suggests a compressive or infiltrative disease of the optic nerve.

 Complete blood count, comprehensive metabolic panel, erythrocyte sedimentation rate, C-reactive protein, and thyroid function tests were normal. Interferon-gamma release assay, HIV antibody, rapid plasma reagin, Lyme antibody, antinuclear antibody, and antineutrophil cytoplasmic antibody (ANCA) tests were negative. A noncontrast computed tomography (CT) scan of the head revealed thickening of the left inferior rectus muscle. Orbital magnetic resonance imaging (MRI) with gadolinium and fluid-attenuated inversion recovery imaging demonstrated a T2 hyperin-



FIG 2. Magnetic Resonance Image. T2-weighted coronal orbital magnetic resonance imaging (MRI) with gadolinium and fluid-attenuated inversion recovery imaging showed a hyperintense, heterogeneous 1.4×1.2×1.2-cm mass in the left inferior rectus muscle (arrow).

tense, heterogeneous 1.4-cm mass in the left inferior rectus muscle (Figure 2). There was no carotid-cavernous fistula, brain mass, or meningeal enhancement.

An isolated mass in one ocular muscle raises the probability of a cancer. The most common malignant orbital tumor is B-cell lymphoma. Metastatic cancer to the eye is rare; breast, prostate, and lung cancer account for the majority of cases. The family history of breast and ovarian cancer raises the possibility of a *BRCA* mutation, which is also associated with gastric, pancreatic, and prostate malignancies. Granulomatosis with polyangiitis may be ANCA negative in localized sino-orbital disease. Biopsy of the orbital mass is the next step.

 The patient underwent transconjunctival orbitotomy with excision of the left inferior rectus mass. Two days later, he presented to the emergency department with acute onset epigastric pain, nausea, and vomiting. A comprehensive review of systems, which had not been performed until this visit, revealed an unintentional 20-lb weight loss over the previous 3 months. He had a progressive ache in the left anterior groin that was dull, tender, nonradiating, and worse with weight bearing. He denied melena or hematochezia.

His temperature was 37 °C; heart rate, 98 beats per minute; and blood pressure, 128/63 mm Hg. He had midepigast-ric tenderness and point tenderness over the anterior iliac spine. White blood cell count was 12,600/ μ L; hemoglobin,

14.5 g/dL; and platelet count, 158,000/ μ L. Serum lipase was 7,108 U/L. Serum creatinine, calcium, and triglyceride levels were normal. Alkaline phosphatase was 117 U/L (normal, 34-104 U/L); total bilirubin, 1.1 mg/dL; alanine aminotransferase (ALT), 119 U/L (normal, 7-52 U/L); and aspartate aminotransferase (AST), 236 U/L (normal, 13-39 U/L). Troponin I was undetectable, and an electrocardiogram demonstrated sinus tachycardia. Urinalysis was normal.

Concomitant pancreatitis and hepatitis with an elevated AST-to-ALT ratio should prompt evaluation of recurrent choledocholithiasis and a repeat inquiry about alcohol use. His medications should be reviewed for an association with pancreatitis. Anterior groin discomfort usually reflects osteoarthritis of the hip joint, inguinal hernia, or inguinal lymphadenopathy. Groin pain may be referred from spinal nerve root compression, aortoiliac occlusion, or nephrolithiasis. Weight loss in the presence of an inferior rectus mass suggests one of the aforementioned systemic diseases with orbital manifestations. Pancreatitis and groin discomfort may be important clues, but the chronicity of the recurrent pancreatitis and the high prevalence of hip osteoarthritis make it equally likely that they are unrelated to the eye disease.

 **CT scan of the abdomen and pelvis with contrast showed peripancreatic edema with fat stranding but no pancreatic or hepatobiliary mass. The common bile duct was normal. A 2.2×1.3-cm mass in the right posterior subphrenic space, a lytic lesion in the left anterior inferior iliac spine, and right nonobstructive nephrolithiasis were identified. CT scan of the chest with contrast showed multiple subpleural nodules and innumerable parenchymal nodules.**

Subcentimeter hilar, mediastinal, and prevascular lymphadenopathy were present, as well as multiple sclerotic lesions in the right fourth and sixth ribs. Prostate-specific antigen was 0.7 ng/mL (normal, $\leq$ 4.0 ng/mL). Cancer antigen 19-9 level was 5.5 U/mL (normal, $<$ 37.0 U/mL), and carcinoembryonic antigen (CEA) was 100.1 ng/mL (normal, 0-3 U/mL).

Widespread pulmonary nodules, diffuse lymphadenopathy, and bony lesions raise concern for a metastatic malignancy. There is no evidence of a primary carcinoma. The lack of hepatic involvement reduces the likelihood of a gastrointestinal tumor, although a rectal cancer, which may drain directly into the inferior vena cava and bypass the portal circulation, could present as lung metastases on CT imaging. Lymphoma is plausible given the diffuse lymphadenopathy and orbital mass. Sarcoidosis and histiocytic disorders (eg, Langerhans cell histiocytosis) also cause orbital disease, pulmonary nodules, lymphadenopathy, and bone lesions, although a subphrenic mass would be atypical for both disorders; furthermore, the majority of patients with adult Langerhans cell histiocytosis smoke cigarettes. The elevated CEA makes a metastatic solid tumor more likely than lymphoma but does not specify the location of the primary tumor.

 **Pathology of the inferior rectus muscle mass showed well-differentiated adenocarcinoma (Figure 3A and 3B). A CT-guided biopsy of the left anterior inferior iliac spine revealed well-differentiated adenocarcinoma (Figure 3C). Adenocarcinoma of unknown primary was diagnosed.**

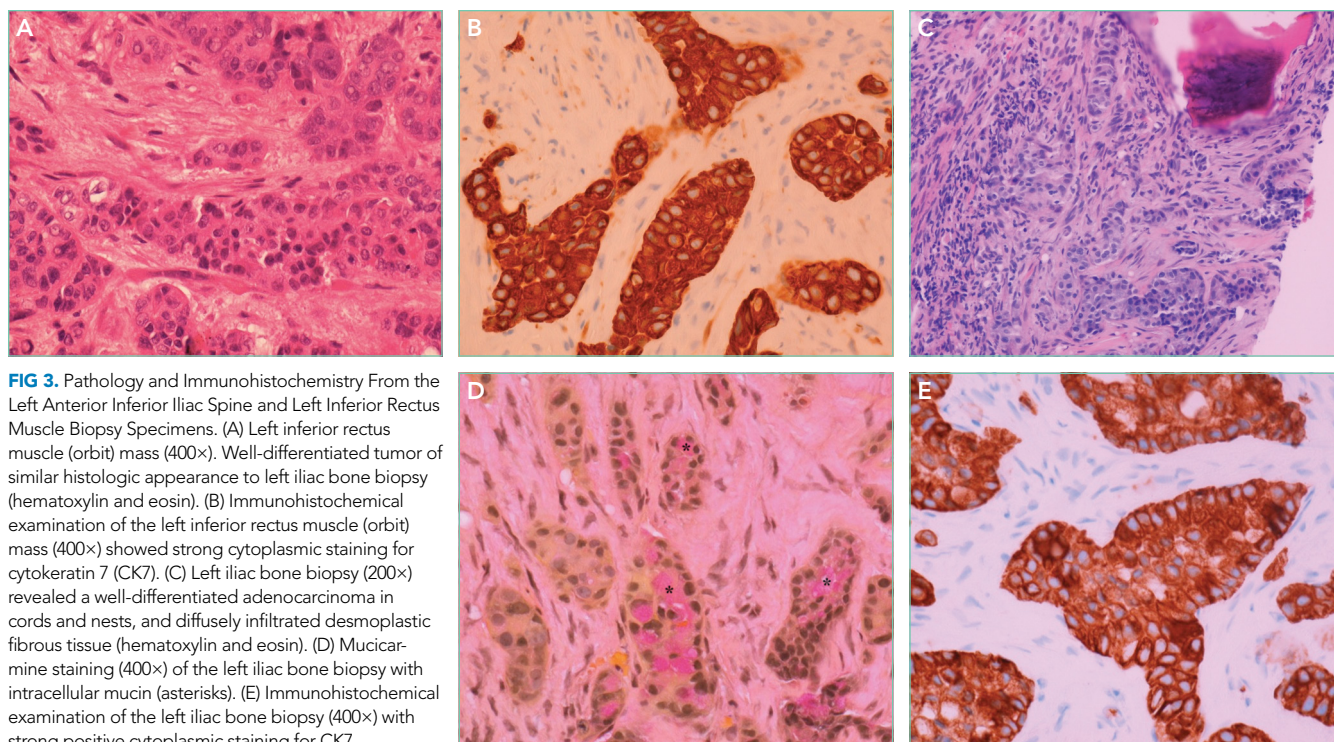


FIG 3. Pathology and Immunohistochemistry From the Left Anterior Inferior Iliac Spine and Left Inferior Rectus Muscle Biopsy Specimens. (A) Left inferior rectus muscle (orbit) mass (400 $\times$). Well-differentiated tumor of similar histologic appearance to left iliac bone biopsy (hematoxylin and eosin). (B) Immunohistochemical examination of the left inferior rectus muscle (orbit) mass (400 $\times$) showed strong cytoplasmic staining for cytokeratin 7 (CK7). (C) Left iliac bone biopsy (200 $\times$) revealed a well-differentiated adenocarcinoma in cords and nests, and diffusely infiltrated desmoplastic fibrous tissue (hematoxylin and eosin). (D) Mucicarmine staining (400 $\times$) of the left iliac bone biopsy with intracellular mucin (asterisks). (E) Immunohistochemical examination of the left iliac bone biopsy (400 $\times$) with strong positive cytoplasmic staining for CK7.

Subsequent immunohistochemical (IHC) staining was positive for cytokeratin 7 (CK7) and mucicarmine (Figure 3D and 3E) and negative for cytokeratin 20 (CK20) and thyroid transcription factor 1 (TTF1). This IHC profile suggested pancreatic or upper gastrointestinal tract lineage. Positron emission tomography–CT (PET-CT) scan was aborted because of dyspnea and chest pressure following contrast administration. He declined further imaging or endoscopy. He received palliative radiation and three cycles of paclitaxel and gemcitabine for cancer of unknown primary (CUP). Two months later, he developed bilateral upper-arm weakness due to C7 and T2 cord compression from vertebral and epidural metastases; his symptoms progressed despite salvage chemotherapy. He was transitioned to comfort care and died at home 9 months after diagnosis.

DISCUSSION

This patient's new headache and ocular abnormalities led to the discovery of an inferior rectus muscle mass. Initially unrecognized unintentional weight loss and hip pain recast a localized orbital syndrome as a systemic disease with pancreatic, ocular, pulmonary, lymph node, and skeletal pathology. Biopsies of the orbital rectus muscle and iliac bone demonstrated metastatic adenocarcinoma. Imaging studies did not identify a primary cancer, but IHC analysis suggested carcinoma of upper gastrointestinal or pancreatic origin.

Acute and chronic pancreatitis are both associated with pancreatic cancer.¹ Chronic pancreatitis is associated with an increasing cumulative risk of pancreatic cancer; a potential mechanism is chronic inflammation with malignant transformation.^{2,3} There is also a 20-fold increased risk of pancreatic cancer in the first 2 years following an episode of acute pancreatitis,⁴ which may develop from malignant pancreatic duct obstruction. Although the post-acute pancreatitis risk of pancreatic cancer attenuates over time, a two-fold increased risk of pancreatic cancer remains after 10 years,⁴ which suggests that acute pancreatitis (particularly when idiopathic) either contributes to or shares pathogenesis with pancreatic adenocarcinoma. In elderly patients without gallstones or alcohol use, an abdominal CT scan or MRI shortly after resolution of the acute pancreatitis may be considered to assess for an underlying pancreatic tumor.⁵

CUP is a histologically defined malignancy without a known primary anatomic site despite an extensive evaluation. CUP accounts for up to 10% of all cancer diagnoses.⁶ CUP is ascribed to a primary cancer that remains too small to be detected or spontaneous regression of the primary cancer.⁷ Approximately 70% of autopsies of patients with CUP identify the primary tumor, which most commonly originates in the lung, gastrointestinal tract, breast, or pancreas.⁸

When a metastatic focus of cancer is found but the initial diagnostic evaluation (including CT scan of the chest, abdomen, and pelvis) fails to locate a primary cancer, the next step in searching for the tissue of origin is an IHC analysis of the tumor specimen. IHC analysis is a multistep staining process that can identify major categories of cancer, including carcinoma (ade-

nocarcinoma, squamous cell carcinoma, and neuroendocrine carcinoma) and poorly or undifferentiated neoplasms (including carcinoma, lymphoma, sarcoma, or melanoma). Eighty-five percent of CUP cases are adenocarcinoma, 10% are squamous cell carcinoma, and the remaining 5% are undifferentiated neoplasms.⁹

There are no consensus guidelines for imaging in patients with CUP who have already undergone a CT scan of the chest, abdomen, and pelvis. Mammography is indicated in women with metastatic adenocarcinoma or axillary lymphadenopathy.⁷ MRI of the breast is obtained when mammography is nondiagnostic and the suspicion for breast cancer is high. Small clinical studies and meta-analyses support the use of PET-CT scans,⁷ although one study found that a PET-CT scan was not superior to CT imaging in identifying the primary tumor site in CUP.¹⁰ Endoscopy of the upper airway or gastrointestinal tract is rarely diagnostic in the absence of referable symptoms or a suggestive IHC profile (eg, CK7–, CK20+ suggestive of colon cancer).⁶

Molecular cancer classification has emerged as a useful diagnostic technique in CUP. Cancer cells retain gene expression patterns based on cellular origin, and a tumor's profile can be compared with a reference database of known cancers, aiding in the identification of the primary tumor type. Molecular cancer classifier assays that use gene expression profiling can accurately determine a primary site¹¹ and have been shown to be concordant with IHC testing.¹² Molecular cancer classification is distinct from genetic assays that identify mutations for which there are approved therapies. Serum tumor markers are generally not useful in establishing the primary tumor and should be considered based on the clinical presentation (eg, prostate-specific antigen testing in a man with adenocarcinoma of unknown primary and osteoblastic metastases).

CUP is classified as favorable or unfavorable based on the IHC, pattern of spread, and serum markers in certain cases.⁶ Approximately 20% of CUP patients can be categorized into favorable subsets, such as adenocarcinoma in a single axillary lymph node in a female patient suggestive of a breast primary cancer, or squamous cell carcinoma in a cervical lymph node suggestive of a head or neck primary cancer.⁷ The remaining 80% of cases are categorized as unfavorable CUP and often have multiple metastases. Our patient's pattern of spread and limited response to chemotherapy is characteristic of the unfavorable subset of CUP. The median survival of this group is 9 months, and only 25% of patients survive longer than 1 year.¹³

Biomarker-driven treatment of specific molecular targets independent of the tissue of origin (tissue-agnostic therapy) has shown promising results in the treatment of skin, lung, thyroid, colorectal, and gastric cancers.¹⁴ Pembrolizumab was the first drug approved by the US Food and Drug Administration based on a tumor's biomarker without regard to its primary location. Data to support this approach for treating CUP are evolving and offer hope for patients with specific molecular targets.

Following the focused neuro-ophthalmologic evaluations, with focused examination and imaging, the hospitalist's review of systems at the time of the final admission for pancreatitis set in motion an evaluation that led to a diagnosis of metastatic

cancer. The risk factor of recurrent pancreatitis and IHC results suggested that pancreatic adenocarcinoma was the most likely primary tumor. As the focus of cancer treatment shifts away from the tissue of origin and toward molecular and genetic profiles, the search for the primary site may decrease in importance. In the future, even when we do not know the cancer's origin, we may still know precisely what to do. But for now, as in this patient, our treatments continue to be based on a tumor that is out of sight, but not out of mind.

KEY TEACHING POINTS

- Acute and chronic pancreatitis are associated with an increased risk of pancreatic adenocarcinoma.
- CUP is a cancer in which diagnostic testing does not identify a primary tumor site. Immunohistochemistry and molecular analysis, imaging, and endoscopy are utilized selectively to identify a primary tumor type.
- Treatment of CUP currently depends on the suspected tissue of origin and pattern of spread.

- Tissue-agnostic therapy could allow for treatment for CUP patients independent of the tissue of origin.

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