A 55-year-old man presented with a 1-year history of dysphagia. He also reported a 6.8-kg (15-lb) weight loss, anorexia, and progressive hoarseness over the previous 6 months. He had no known medical conditions and did not take any medications. His family history was notable for esophageal cancer in his father and paternal uncle. Physical examination of the head and neck revealed no oral leukoplakia, mass, lymphadenopathy, or tenderness on palpation. Examination of the hands and feet revealed digital clubbing along with palmoplantar keratoderma, findings that are consistent with tylosis (Panels A and B). His father had had similar skin changes on his palmoplantar surfaces. Computed tomography of the chest showed a circumferential mass involving the proximal esophagus (Panel C). Upper endoscopy showed a large ulcerated mass in the upper third of the esophagus that spanned 10 cm and was partially obstructive. Pathological examination revealed invasive, poorly differentiated squamous-cell carcinoma (Panel D; hematoxylin and eosin stain). Tylosis and squamous-cell carcinoma of the esophagus can be observed in hereditary conditions such as the Howell–Evans syndrome. Unfortunately, the patient’s condition deteriorated during his hospitalization, and he died from an aspiration event before further testing could be pursued.