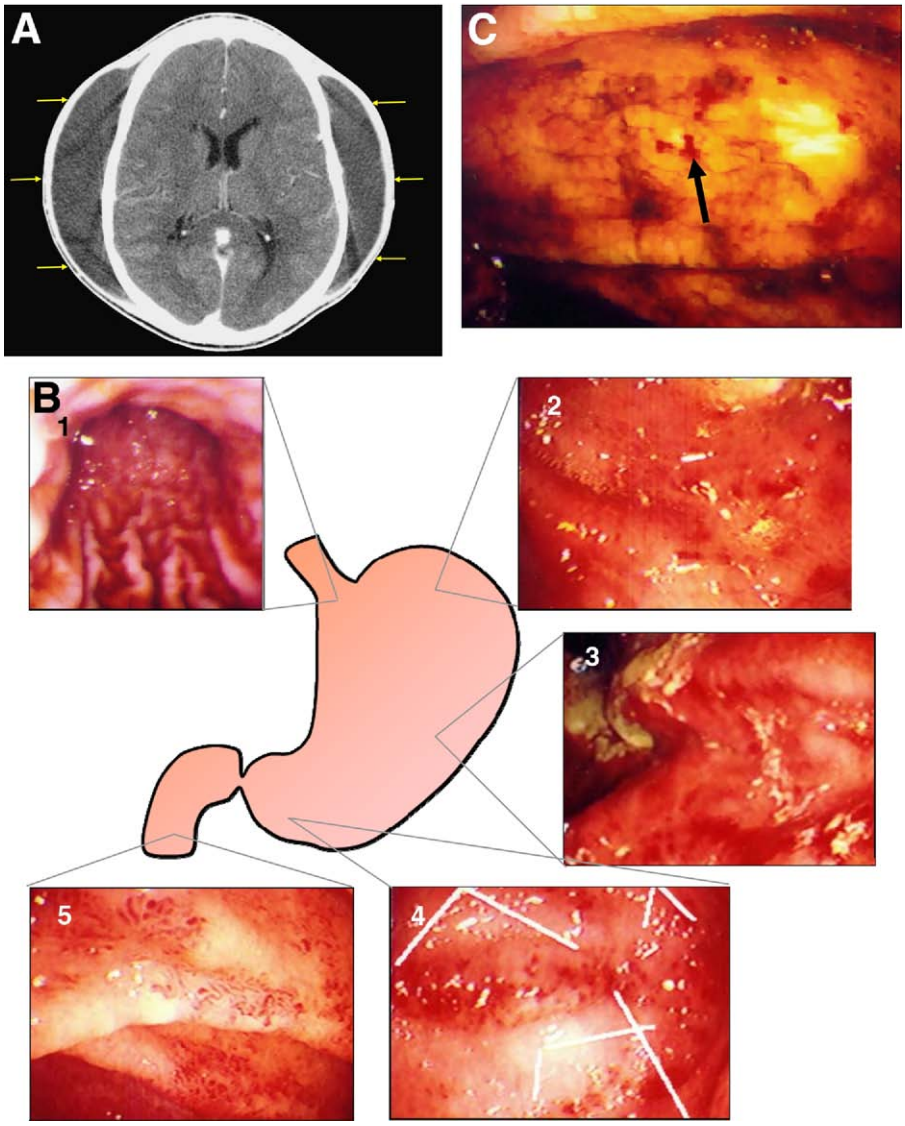
Image 2



Question: A 17-year-old boy presented with a swollen head. One month earlier, he had been hit in the head with a basketball during a game, and he had developed progressive swelling a few days later. The patient did not have any history of bruising or bleeding except recurrent, self-limited epistaxis, but he did have a history of fever (up to 39°C), 30-kg weight loss, and pancytopenia (in the presence of trilineage cellular hypoplasia on bone marrow biopsy) that lasted 4 months after contracting infectious mononucleosis (seroconversion confirmed by positive immunoglobulin [Ig]M antibodies) treated with the antiviral agent cidofovir. The patient also had a prior history of refractory iron-deficiency anemia (not alleviated by oral iron therapy). The maternal grandfather (age 72 years) had the same gastroduodenal condition, severe refractory iron-deficiency anemia requiring intravenous iron therapy, and bilateral renal artery and aortic aneurysms. The mother was healthy, and a sister (age 22 years) was healthy except for a borderline low platelet count.

Physical examination showed circumferential symmetrical enlargement of the head, accentuated at the temples, with a subcutaneous fluctuant fluid collection. He had slightly prominent eyes, a pinched nose, a webbed neck, kyphosis, hyperextensible digits, and pectus excavatum. He also had splenomegaly, mildly extensible and translucent skin without a history of

poor wound healing, and numerous 1-mm telangiectatic lesions on the trunk and legs. Laboratory analyses revealed anemia, thrombocytopenia, and mildly elevated lactate dehydrogenase and aspartate aminotransferase levels (Table 1). On biopsy, the bone marrow was hypocellular (25% cellularity) with low iron stores and diploidy, no Epstein–Barr virus (EBV) particles were detected, and normal, adequate megakaryocytes were present. A non–contrast-enhanced computed tomography (CT) scan of the head was obtained (Figure *A*). Gastroduodenal endoscopy (Figure *B*) and colonoscopy (Figure *C*) were performed. His older brother had presented with severe pancytopenia owing to aplastic anemia and iron malabsorption at age 16 years. He had pectus excavatum, hyperextensible finger joints, avascular necrosis of the hips and shoulders, and similar gastroduodenal abnormalities. The brother died 2 years later of massive intracranial hemorrhage.

What is your diagnosis from the CT scan (Figure *A*)? What is your diagnosis from the gastroduodenal endoscopy (Figure *B*) and colonoscopy (Figure *C*)? What is the patient's condition?

See the GASTROENTEROLOGY web site (www.gastrojournal.org) for more information on submitting your favorite image to Clinical Challenges and Images in GI.

FADI BRAITEH, MD
RAZELLE KURZROCK, MD
Department of Investigational Cancer Therapeutics
Phase I Program
Division of Cancer Medicine
The University of Texas M. D. Anderson Cancer Center
Houston, Texas and
The University of Texas Graduate School of Biomedical Sciences
Houston, Texas

The authors thank Ms Melissa Burkitt for assistance in editing this manuscript.

Conflicts of interest

The authors disclose no conflicts.

0016-5085/09/$36.00
doi:10.1053/j.gastro.2008.11.013

Table 1. Laboratory Test Results

Parameter	Value	Normal
Hematologic counts and coagulation		
White cells ($\times 10^6$/l)	3,800	4–11,000
Polynuclear cells (%)	46	42–66
Lymphocytes (%)	32	24–44
Mononuclear cells (%)	14	2–7
Eosinophils (%)	5	1–4
Platelets ($\times 10^6$/l)	53,000	150–350,000
Hemoglobin (g/dl)	9.9	14.0–18.0
Mean corpuscular volume (fl)	71	82–98
Prothrombin time (sec)	11.8	11.4–14.01
Partial thromboplastin time (sec)	24.0	22.0–35.0
Serum chemistry		
Sodium (mmol/l)	135	135–147
Potassium (mmol/l)	42	3.5–5.0
Chloride (mmol/l)	102	98–108
Carbon dioxide (mmol/l)	28	23–30
Urea nitrogen (mg/dl)	8	8–20
Creatinine (mg/dl)	0.6	0.8–1.5
Calcium (mg/dl)	8.5	
Zinc (mcg/dl)	46	60–130
Serum liver enzymes		
Alkaline phosphatase (IU/l)	116	38–126
Aspartate aminotransferase (IU/l)	104	15–46
Alanine aminotransferase (IU/l)	48	7–56
Total bilirubin (μg/dl)	0.8	0–1.0
Lactate dehydrogenase (IU/l)	1005	313–618
Albumin (g/dl)	3.3	3.5–5.0
Anemia workup		
Iron level (μg/dl)	71	49–181
Transferrin (mg/dl)	275	188–341
Ferritin (ng/ml)	856	22–322
Red blood cell folate (ng/ml)	616	229–703
Vitamin B_{12} (pg/ml)	567	211–911
Reticulocytes (%)	1.2	0.5–1.5
Erythropoietin level (mU/ml)	71	<25
Ham's acid PNH test	Negative	Negative
Coombs direct and indirect	Negative	Negative
Other		
Cytogenetics	46,XY	46,XY
CD4 (UL)	419	
CD8 (UL)	622	
HIV-1 and -2 (ELISA)	Nonreactive	Nonreactive
Hepatitis A, B, and C	Nonreactive	Nonreactive
CMV (serology)	Negative	Negative
EBV viral capsid antigen IgG	1:1280 ↑	<1:10
EBV viral capsid antigen IgM	<1:10	<1:10
EBV nuclear antigen	1:250	<1:4
EBV early antigen IgG	369	0–119
IgG (ng/dl)	1600	624–1,680
IgA (ng/dl)	512	74–327
IgM (ng/dl)	135	29–214
H pylori (serology)	Negative	Negative
Antiplatelet Ab	Negative	Negative
Brucella (serology)	Negative	Negative
Bartonella (serology)	Negative	Negative

Answer to the Clinical Challenges and Images in GI Question: Image 2: Extensive Bilateral Extracranial Subcutaneous Fluid Collection

An extensive bilateral extracranial subcutaneous fluid collection (Figure *A*, *arrows*) was responsible for the swelling that prompted presentation. The cystic component superiorly and more solid-appearing blood clotting inferiorly was consistent with extracranial subgaleal hematoma. No intracranial fluid collection or skull fracture was evident. A cerebral magnetic resonance angiogram (MRA) and CT scans of the chest, abdomen, and pelvis were normal.

The patient was treated by transcutaneous needle aspiration, which returned a motor-oil–like fluid consistent with old, hemolyzed blood. The hematoma resolved and did not reaccumulate. The upper gastroduodenal endoscopy revealed vascular ectasia in the stomach and numerous telangiectases in the duodenum (Figure *B*), and the colonoscopy showed cecal vascular ectasias (Figure *C*, *arrow*).

Possible diagnoses considered were Ehlers–Danlos syndrome disease and hereditary hemorrhagic telangiectasia, but not all the patient's clinical features were consistent with these syndromes (Table 2).[1] The patient was referred for genetic counseling and testing, but without a final identifiable diagnosis. The patient died at home 1 year later of massive intracranial hemorrhage, possibly secondary to a ruptured cerebral aneurysm not visualized on the cerebral MRA performed earlier. Permission for an autopsy was not granted.

This patient and his brother seem to have a new syndrome with some features of both Ehlers–Danlos syndrome (hyperextensible and translucent skin, hypermobile joints, and dysmorphic facial features)[2] and hereditary hemorrhagic telangiectasia (mucosal and skin telangiectases, iron-deficiency anemia, and mucosal and brain arteriovenous malformations)[3] plus unique signs such as dysmorphic musculoskeletal anomalies (kyphosis and pectus excavatum), iron malabsorption, bone marrow failure, arterial aneurysms, and avascular necrosis of the hips. A suggested name for the syndrome is "familial DELTA PHI syndrome," emphasizing the combination of *d*ysmorphic features, *e*pistaxis, *l*axity of joints, *t*elangiectasia, *a*neurysms, *p*ancytopenia, *h*yperextensible skin, and *i*ron malabsorption. Further cases remain to be identified and genetic exploration is warranted for identification of the molecular pathophysiology.

References

1. Parapia LA, Jackson C. Ehlers-Danlos syndrome—a historical review. Br J Haematol 2008;141:32–35.
2. Gawthrop F, Mould R, Sperritt A, et al. Ehlers-Danlos syndrome. BMJ 2007;335:448–450.
3. Abdalla SA, Geisthoff UW, Bonneau D, et al. Visceral manifestations in hereditary haemorrhagic telangiectasia type 2. J Med Genet 2003;40:494–502.

Table 2. Distinctive and Shared Features of the Clinical Case Presented, Ehlers–Danlos Syndrome, and Hereditary Hemorrhagic Telangiectasia

Clinical Features	Ehlers-Danlos Syndrome, Classic or Vascular Type (Type IV)	Hereditary Hemorrhagic Telangiectasia Types 1 and 2 (Rendu–Osler–Weber Syndrome)	Patient Presented (DELTA PHI Syndrome)
Blood vessels	Fragile blood vessels and organs that are prone to rupture secondary to defects in fibrillar–collagen metabolism	Mucosal telangiectases are universal, occur as early as age 10–21 y, but are more severe after age 40; typically affecting nasal mucosa, with various degrees of epistaxis (90%)	Telangiectases of the mucosa of the nose with epistaxis (in early teens)
Skin	—	Skin telangiectases are universal but occur later in life, typically on tongue, lips, conjunctiva, arms and trunk, fingertips, nails, and ears (13%–89%)	Telangiectases of skin
	Fragile skin that bruises easily, delayed healing and atrophic scars	—	—
	Thin, translucent skin (veins visible beneath)	—	Thin, translucent skin (veins visible beneath)
	Hyperextensible skin	—	Hyperextensible skin
Mucosa	—	AVM predominate in certain forms: pulmonary AVM (5%–15%) causing hemoptysis and right-to-left shunting (cyanosis, clubbing, bruit cerebral abscesses, paradoxical emboli); hepatic AVM (8%–30%) causing high-output heart failure and portal hypertension; brain and spinal AVM (5%–11%) causing seizure, intracerebral hemorrhage, and headache	Family history of aortic and renal arterial aneurysms (grandfather) and intracranial aneurysms (brother and patient)
	—	GI telangiectases, AVM (11%–40%), and iron-deficiency anemia; bleeding is rare and occurs after fifth decade (<2%)	Gastrointestinal telangiectases; both patient and brother had bleeding in their teens
	—	—	Kyphosis, webbed neck, pectus excavatum
Joints	Hypermobility of joints (usually limited to the fingers and toes)	—	Hypermobility of joints (fingers and toes)
Maxillofacial	Distinctive facial features: sunken cheeks and small chin	—	Facial changes, small chin
	Protruding eyes	—	Prominent eyes
	Thin nose and lips	—	Mildly pinched, thin nose
Family history	—	—	Colonic diverticula, but no upper GI diverticula
	—	—	Aortic, renal, and brain aneurysms
	—	—	Avascular necrosis of hips and shoulders in brother
Laboratory and genetic findings	—	Iron-deficiency anemia from epistaxis	Iron-deficiency anemia
	—	—	Iron malabsorption
	—	—	Bone marrow failure with pancytopenia: thrombocytopenia, leukopenia
	Genetically heterogeneous group: (1) Autosomal-dominant disorder (classic variant), mutations in *COL3A1* gene; (2) homozygous tenascin-X gene (*TNXB*) mutations or deletions	Autosomal-dominant disorder: Mutations in *ACVRL1*, *ENG*, and *SMAD4* genes	Unknown, suspected