Grand Rounds November 18

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A man with leukemia

Case History

- **HPI**: 52 year old male with no past medical history presented to the Brooklyn VA ER on **7/27/10** stating he "is extremely tired." He appears pale.
- **Vitals**: **T 100.3, P 101**, R 16, BP 117/76, 100% RA
- **Labs**: **WBC 1.1 RBC 1.28 HGb 4.0, HCt 12.0, Plt 10** Neut 10%, Segs 11%, Lymph 62%
  - Blood culture, UA, and CXR normal
- **PMH**: none
- **ROS**: Pt had recent I&D of abdominal wall abscess at outside hospital and was started on Keflex and **Bactrim DS** for 7 days , completed course prior to presentation
- **Assessment**: symptomatic anemia, pancytopenia, and neutropenic fever

Case History (cont'd)

- **Plan:**
  - Pt started on broad-spectrum IV antibiotics, given pRBCs and platelets and admitted to medicine
  - Differential for severe pancytopenia includes: drug-induced from Bactrim DS versus leukemia.
    - However, relatively mild symptoms implies a chronic course so leukemia is more likely explanation
    - Peripheral blood smear does not show leukemic cells
    - Bone marrow biopsy and aspiration required for work up
- The patient denies anything is wrong and refuses BM biopsy

Hospital course

- Pt asked daily about bone marrow biopsy but consistently refuses
- Received transfusions of pRBC x 5, PLT x 3
- HIV, hepatitis panel negative
- Discharged on **08/02** on neupogen & levaquin
- Labs on discharge: **WBC 3.5, RBC 2.82, HGb 9.1, HCt 25.8, Plt 31**
- Told to follow up with Heme-Onc clinic as an outpatient

Post-Hospital course

- Pt follows up weekly in heme-onc clinic, is treated with transfusions, neupogen, and antibiotics.
- Continues to refuse bone marrow biopsy until **8/23/10**, nearly 1 month after presenting to the ER
- Pt undergoes biopsy and aspirate analysis with flow cytometry and FISH

Patient care, medical knowledge, systems-based practice

Results & Interpretation

- **Bone Marrow Biopsy (8/31/10):**
  - "Abnormal immature myeloid population that expresses CD11, CD11B, CD14, CD64, HLADR, CD33, with smaller expression of other antigens. Review of the marrow core shows a hypercellular marrow with a complete shift to immature cells. Rare neutrophils are seen. Megakaryocytes are present. History of being on neupogen for 8 days is noted. These results, in conjunction with the morphology, favor an acute myelogenous leukemia showing monocytic diferentiation."
- **Cytogenetics and FISH:**
  - Trisomy 21, chromosome 17 abnormalities, no 15:17 translocation, 82.5% nuclei positive for 3 AML1 gene hybridization signals
- **All findings point to: M4, myelomonocytic subtype of AML**

Patient care, medical knowledge, practice-based learning

Rehospitalization

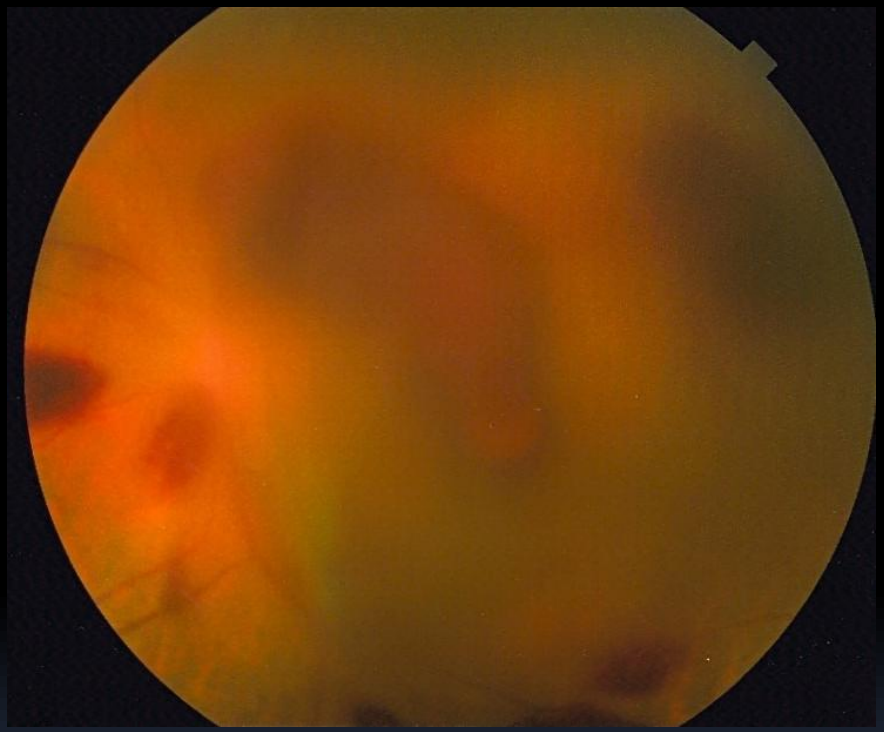
- Pt re-admitted on **09/07** for induction chemotherapy with Cytarabine + Idarubicin (7+3 regimen 1)
- **09/23/10, Hospital Day 17 (2 weeks prior to presentation)**
  - Housestaff note:
    - Pt examined at bedside. Looks ill, states he does not feel well. c/o worsening cough, sputum production, febrile, (+) diarrhea
    - Labs: **WBC 0.1, RBC 2.16, HGb 6.7, HCt 18.4, Plt 10**
    - Exam: pupils equally round and reactive to light
- **10/07/10, Hospital Day 31**
  - Housestaff note:
    - Pt complains of blurry vision in his left eye, has lasted approximately 2 weeks (since **09/23/10**, note labs above)
    - Labs: **WBC 0.8, RBC 2.46, HGb 7.6, HCt 21.2, Plt 14**
    - Exam: pupils equally round and reactive to light

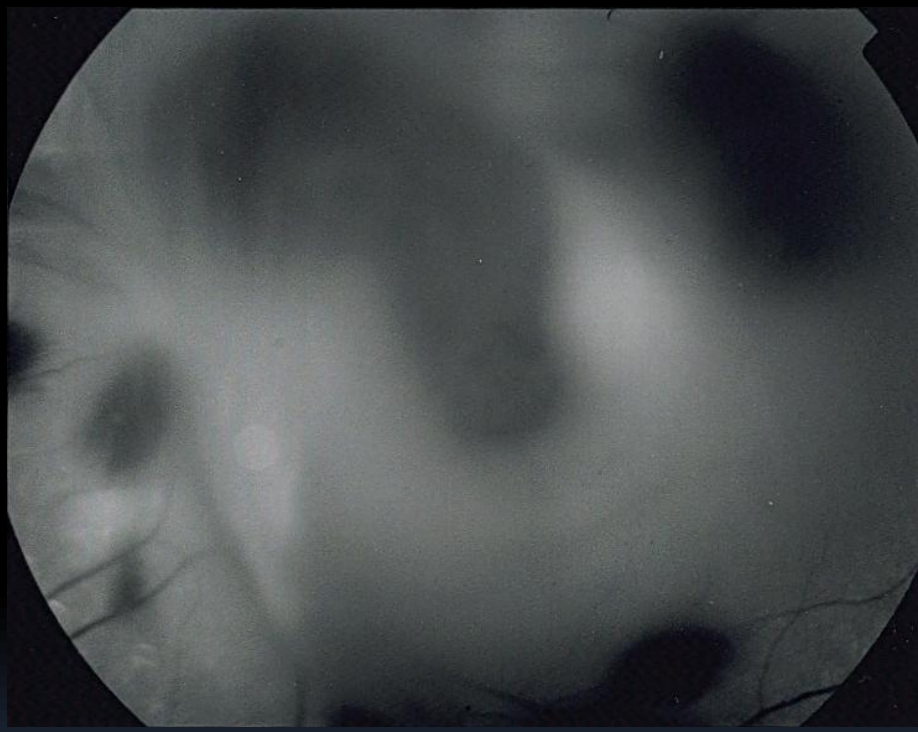
Initial evaluation 10/08/10

- Patient seen at bedside
- **CC:** blurry vision OS x **2 weeks (since 9/17/10)**
- **HPI:** Pt states his vision in the left eye became blurry and remained that way. He is unable to identify an exact moment he noticed the problem.
- **Exam**
  - **Nva-sc:** 20/25- OD; CF at 3 ft ph NI OS
  - **P:** 3-2 no APD OU
  - **EOM**: full, no pain or diplopia
  - **CVF**: grossly full OU

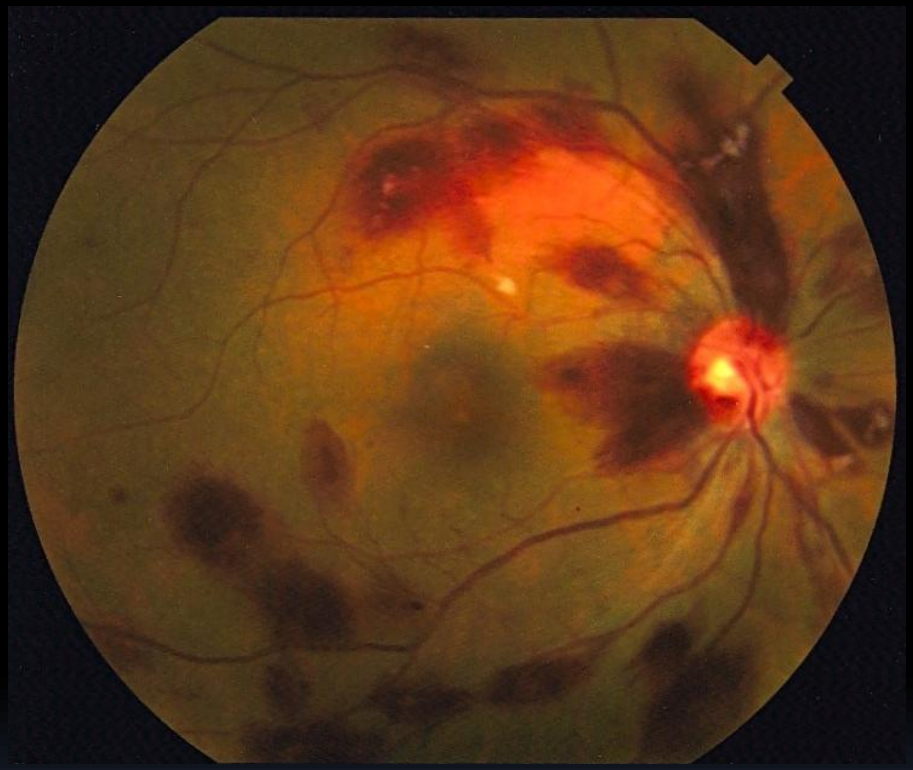
Initial evaluation (cont'd)

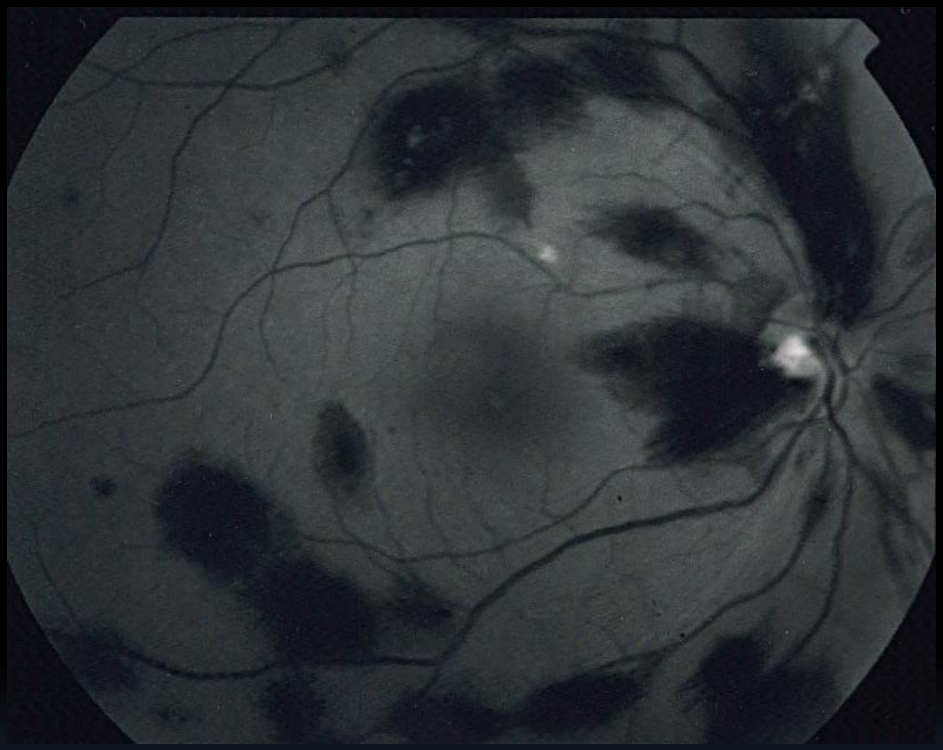
- **PLE** (pt pancytopenic, in isolation)
  - LLA: wnl OU
  - C/S: w&q OU
  - K: clear OU
  - AC: flare & cells OU
  - I/P: BRR OU (-) APD
  - L: clear OU
- **DFE**
  - Results after photos on next slide
- **Color plates:** full OD; unable to assess OS secondary to Va
- Pt comes to clinic 10/13/10 in reverse isolation
  - Fundus photos taken, see next slide





Patient care, medical knowledge





Patient care, medical knowledge

Initial evaluation (cont'd)

- **DFE**
  - V: clear OD; hemorrhage OS
  - M:
    - OD: flat, multiple round areas of hemorrhage, white-centered hemorrhage inferior to superior arcade, hard exudate vs CWS superior
    - OS: hazy view, but few preretinal or retinal hemorrhages appear visible behind vitreous hemorrhage, including one large hemorrhage possibly involving the macula
  - C/D:
    - OD: 0.3, hemorrhages extending from disc nasally, temporally toward macula, and superiorly along superior arcade, white-centered hemorrhage nasal to disc
    - OS: cannot make out optic nerve details secondary to vitreous hemorrhage
  - V/P: normal caliber, several large round hemorrhages, including white-centered hemorrhages surrounding vessels, d/b heme OU

Retinal hemorrhage: DDx

- Trauma
  - Tear, shaken baby syndrome, detachment
- Infectious/inflammatory
  - Subacute bacterial endocarditis, CMV retinitis, histoplasmosis, posterior uveitis,
- Neoplastic
  - Retinoblastoma, Leukemia
- Metabolic/Endocrine/Autonomic
  - Diabetic retinopathy, Generalized Gangliosidosis, Iron deficiency Anemia, hypertensive retinopathy
- Vascular
  - SAH, cavernous sinus thrombosis, retinal embolism, retinal vein thrombosis
- Eale's disease
- Coagulopathies
- Sickle cell disease
- Ischemic optic neuropathy

Vitreous hemorrhage: DDx

Proliferative diabetic retinopathy
Posterior vitreous detachment
Trauma (blunt or penetrating, including shaken baby syndrome/child abuse)
Retinal tear
Retinal vein occlusion
Hypertensive retinopathy
Subarachnoid hemorrhage (Terson syndrome)
Avulsed retinal vessels
Age-related macular degeneration
Radiation retinopathy
Macroaneurysms
Thrombocytopenia
Leukemia

Assessment and Plan

- Blurry vision in left eye
  - Vitreous hemorrhage in the left eye and retinal hemorrhage in both eyes likely related to patient's abnormal hematologic parameters, especially his severe thrombocytopenia, which are due to his underlying leukemic process
  - Optic nerve infiltration is unlikely as patient has no APD in the left eye, and normal nerve appearance and color vision in the right eye
  - Based on review of the literature, no acute intervention is recommended
  - Recommend continuing treatment of patient's leukemia with goal to normalize hematologic parameters
  - Will monitor closely for optic nerve infiltration and consider radiation treatment or neurological imaging at a later date
  - RD precautions given

Patient care, medical knowledge, practice-based learning

Followup exam 10/13/10

- DVa sc: 20/40-2 ph 20/20- OD; CF @ 3ft ph NI OS
- P: 3-2, no APD OU

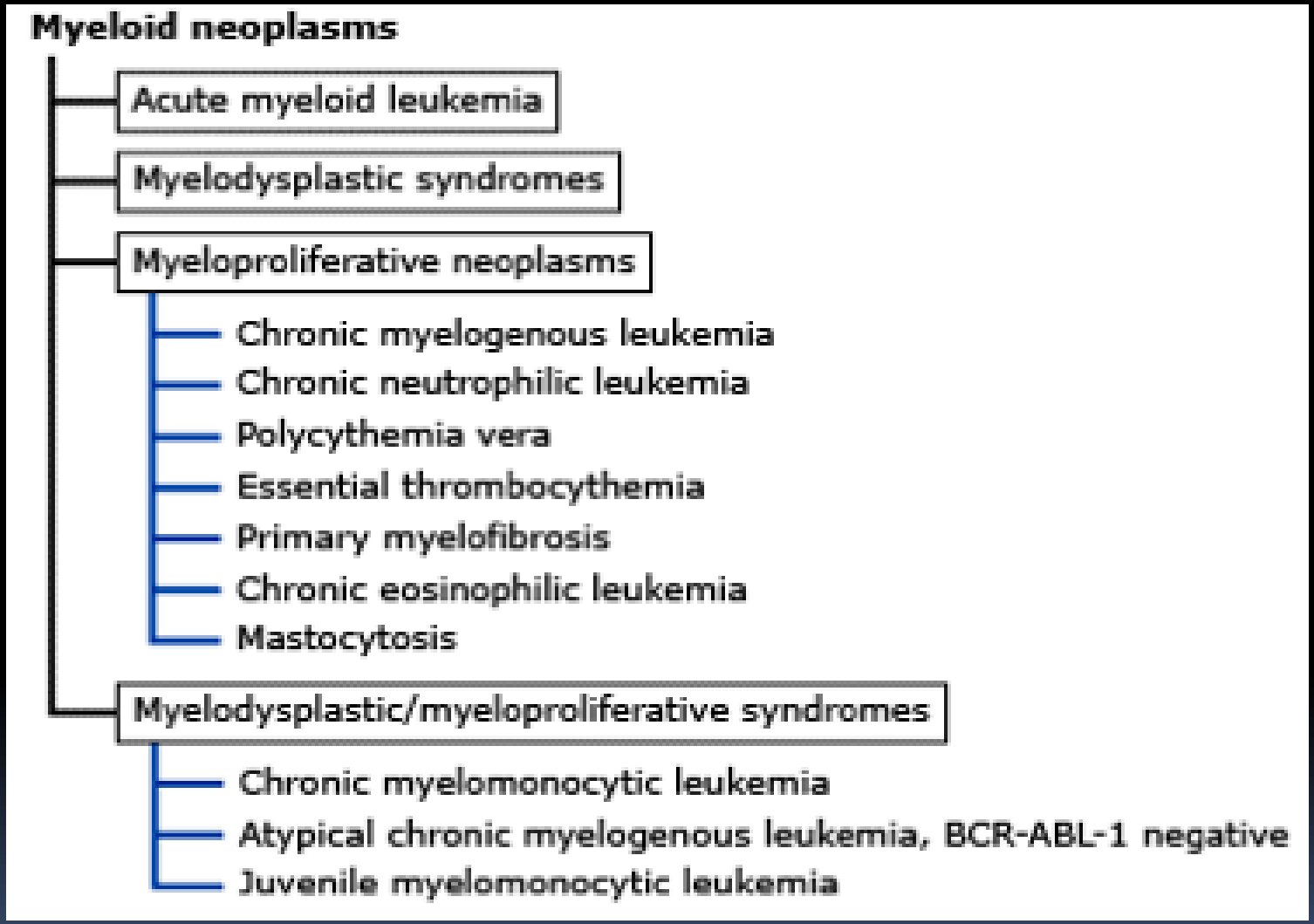
Patient care, medical knowledge

The leukemias: classification

- Broad categories: **Lymphoid** or **Myeloid**, **Acute** or **chronic**
- Further classified by cell of origin, and based on flow cytometry, immunohistochemistry, and cytogenetics
- **CML**
  - **14% of all leukemias**
  - Philadelphia chromosome (9:22 translocation) seen in 90%
  - Patients usually **asymptomatic** at diagnosis
- **CLL**
  - **29% of all cases, Increasing incidence with age**
  - 95% involve B-cell lineage
  - Patients usually **asymptomatic** at diagnosis
- **ALL**
  - **11% of all cases**
  - **Most common malignancy in children**
  - Patients present with progressive weakness, infections, bleeding
- **AML**
  - **46% of cases**
  - Worse prognosis than ALL
- Global 5-year survival is 20% for all leukemias taken together

Patient care, medical knowledge, practice-based learning

Hematologic malignancies in context



Patient care, medical knowledge, practice-based learning

AML: definition and pathophysiology

- Acute myeloid leukemia, aka acute myelogenous leukemia, aka acute non-lymphocytic leukemia
  - Hematopoietic neoplasms involving myeloid line precursor cells
  - Characterized by clonal proliferation of myeloid precursors with reduced capacity to differentiate into more mature elements
    - This results in accumulation of leukemic blasts in the bone marrow, peripheral blood, and other tissues
    - Also causes reduction in RBC, platelet, and mature granulocyte production

AML: diagnosis

- Based on bone marrow biopsy and morphologic, cytochemical, immunophenotypic, and cytogenic/molecular analysis
- AML should be classified into subtype
  - Two common classification systems: **FAB (French-American-British)** and WHO systems
  - FAB system more common
  - Classification based on cell type and degree of maturity

AML: subtypes

Subtype	Name	Frequency	Cell Characteristics
M0	Myeloblastic	9-12%	Extremely immature leukemia cells with no characteristics of differentiated cell
M1	AML with minimal maturation	16-26%	Immature myeloid cells (blasts) are main subtype
M2	AML with maturation	20-29%	Many blasts, but more maturity than M1
M3	Promyeloctic (APL)	1-6%	Immature cells, between myeloblast and myelocyte stage, looks more like white cell
M4	**Acute myelomonocytic**	**16-33%**	**Mix of granulocytic and monocytic cells, more mature than M3**
M5	Acute monocytic leukemia	9-26%	>80% monocytes at different maturity stages
M6	Acute erythroid leukemia	1-4%	Leukemic cells are immature with characteristics of RBCs
M7	Acute megakaryocytic leukemia	0-2%	Leukemic cells are immature with characteristics of platelets

AML: systemic presentation

- Clinical presentation related to complications of pancytopenia
  - Weakness, pallor, easy fatigability, infections, hemorrhagic findings (gingival bleeding, ecchymoses, epistaxis, menorrhagia, etc)
  - Combinations of these symptoms are common
  - Bleeding is based on thrombocytopenia, other platelet disorders, or coagulopathies
  - Approximately 75% of patients with AML will have platelet counts below 100, 25% will have counts below 25 at diagnosis
    - Morphologic and functional abnormalities are seen
    - Prophylactic platelet transfusions given at counts below 10

AML: clinical signs

- **Skin**
  - **Pallor, petechiae, ecchymoses** secondary to thrombocytopenia, DIC, infiltrative lesions suggestive of leukemic involvement (leukemia cutis or myeloid sarcoma)
  - Occurs in 13% of patients
  - Lesions are usually nodular and violaceous/gray-blue
- **CNS**
  - CNS involvement at the time of diagnosis is unknown because routine evaluation of patients without symptoms is not recommended
  - Difficult to predict CNS involvement over the course of treatment, though use of cytarabine is associated with CNS involvement of leukemic cells

AML: clinical signs (cont'd)

- **Oropharynx**
  - Gingival hypertrophy, candidiasis, herpetic lesions
- **Organomegaly**
  - lymph node enlargement, hepatomegaly and splenomegaly are uncommon and suggest possible acute lymphoblastic leukemia
- **Joints**
  - 4% present with symmetric or migratory polyarthritis/arthralgia and bone pain/tenderness

AML: treatment

- Depends on subtype, morphology, and cytogenetics of AML
- Chemotherapy
  - Mainstay of therapy: IV or intrathecal
  - Divided into 3 stages: **induction, consolidation, and maintenance** (maintenance therapy not commonly used in AML)
  - Induction: goal is complete remission
    - Normalization of blood counts, disappearance of leukemic cells from marrow, resolution of signs and symptoms
    - Most common regimen: cytarabine over 7 days along with an anthracycline drug (danorubicin or idarubicin) over 3 days ("7+3")
    - Induction requires 3-5 weeks of hospitalization
    - Our patient treated with cytarabine+idarubicin (7+3) regimen

AML: treatment (cont'd)

- **Allogenic stem cell transplant**
  - From donor with exact HLA match
  - Allows more intensive chemotherapy to be given and achieve higher kill rates
  - Donor immune cells can attack residual AML cells (graft vs leukemia, GVL)
  - But graft vs host disease (**GVHD**) is a risk
- **Autologous stem cell transplant**
  - Healthy peripheral or marrow cells are harvested during remission and stored for later transplantation
  - **No GVL effect, but also no GVHD effect**

AML: Ocular involvement

- Mechanism of ocular findings related to:
  - 1) Direct infiltration of neoplastic cells
  - 2) Hematologic parameters: anemia, thrombocytopenia, or hyperviscosity
  - 3) Opportunistic infections
  - 4) Graft versus host disease from allogenic transplant
- Any ocular structure can be involved in leukemia
  - Retina most commonly involved
  - Anterior segment findings are rare but can represent extramedullary site of relapse
    - Change in iris color, iris nodules, hyphema, hypopyon, glaucoma, sterile corneal ring ulcer, and pannus have been described

AML: Ocular involvement (cont'd)

- Eye findings were much more common prior to advent of effective chemotherapy regimens
- Leukemic cells can infiltrate the conjunctiva and lacrimal glands, producing palpable masses

AML: Ocular involvement (cont'd)

- **Lids**: ectropion, **edema**, mechanical ptosis
- **Conjunctiva**: chemosis, mass, **corkscrew vessels**, conjunctivitis
- **Cornea**: keratitis, limbal infiltration**, sterile ring ulcers**, pannus, melt, dry eye, epithelial changes secondary to chemotherapy
- **Orbit: exophthalmos, orbital/preseptal cellulitis, endophthalmitis, dacryocystitis**
- **Iris, angle, AC, lens**: glaucoma, **uveitis**, hyphema, pseudohypopyon (yellow/gray), heterochromia, cataract secondary to treatment
- **Retina**: hemorrhage, infiltrate, retinitis, vitreous hemorrhage, MA, CWS, peripheral NV, detachment
- **Choroid:** thickening, serous detachment
- **Optic nerve & CNS**: N/V, lethargy, seizures, diplopia, papilledema, blurred vision, **optic nerve infiltration (more common in ALL in children – requires emergent radiation)**
- **Miscellaneous**: anterior segment ischemia, **lacrimal gland infiltration**

AML: Ocular involvement (cont'd)

- In total, only 2 major studies have examined ophthalmic findings in newly diagnosed leukemias of any type
- Autopsy data indicate that **ophthalmic involvement may be higher than widely believed** due to histologic findings that do not correlate to clinical findings
- Wilmer study of postmortem eyes with abnormal findings related to leukemia: 190/233 **(82%) of acute leukemias**

Schachat AP, Markowitz JA, Guyer DR, et al: Opthalmic manifestations of leukemia. Arch Ophthalmol 107:697-700, 1989

Karesh JW, Goldman EJ, Reck K, et al: A prospective opthalmic evaluation of patients with acute myeloid leukmia: Correlation of ocular and hematologic findings. J Clin Oncol 7:1528, 1989

AML: Ocular involvement (cont'd)

- One comprehensive, prospective study of 53 newly diagnosed adults with AML found retinal abnormalities in 44% of cases
- **Retinal hemorrhages** and **cotton wool spots** due to nerve fiber layer ischemia were the most common findings
- Occurrence unrelated to age, AML subtype, WBC count, or hematocrit
- Initial platelet counts were lower in patients with retinopathy
- 10 patients had decreased visual acuity, including 5 with macular hemorrhage
- Definite leukemic retinal infiltration could not be confirmed in the study

Karesh, JW, Goldman, EJ, Reck, K, et al. A prospective ophthalmic evaluation of patients with acute myeloid leukemia: Correlation of ocular and hematologic findings. J Clin Oncol 1989; 7:1528.

AML: Retinal findings

- Retinal findings most often due to anemia & thrombocytopenia
- Most common site of ocular involvement, up to 69% of patients will show retinal findings
- Most commonly occur in the posterior pole, but can be found at any level with occasional extension to the vitreous or subretinal space
- Flame-shaped, dot-blot, and white-centered intraretinal, subretinal, or subhyaloid hemorrhages can be seen

AML: Retinal findings (cont'd)

- Leukemic retinal infiltrates are collections of leukemic cells that appear as grayish white nodules often surrounded by hemorrhage
- "White-centered hemorrhage:"
  - White center may represent localized accumulations of leukemic cells, but platelet-fibrin material or septic emboli may have the same appearance
- Kuwabura and Aiello report a case of AML with miliary nodules of leukemic myelocytes in the retina
  - Mitotic figures seen in these nodules, suggesting active division of malignant cells in the retina
  - The vitreous was uninvolved in this patient, a finding the authors attributed to the barrier function of the ILM

Kuwabara T, Aiello L: Leukemic miliary nodules in the retina. Arch Ophthalmology 72:494-497, 1964

Leukemic retinopathy vs infiltrate

- Important to distinguish between the two for prognostic and therapeutic considerations
- "Leukemic retinopathy"
  - Refers to fundus manifestations of anemia, thrombocytopenia, and hyperviscosity
  - Most commonly seen in patients in relapse
  - Karesh et al showed in their series of patients with AML that lower platelet counts correlated with retinopathy, but hematocrit levels did not correlate
  - Retinopathy in and of itself is not an unfavorable prognostic sign
- "Leukemic infiltrates"
  - May imply poorer prognosis and CNS involvement
  - Most often seen in children with ALL
  - Optic nerve involvement requires emergent radiation

Karesh JW, Goldman EJ, Reck K, et al: *A prospective opthalmic evaluation of patients with acute myeloid*

AML: Retinal findings (cont'd)

- **Cotton-wool spots are occasionally the presenting sign** in adults and can initiate a work-up for leukemia
  - Likely from nerve fiber layer infarcts secondary to ischemia due to viscosity and anemia (4)
- Findings due to viscosity:
  - Tortuosity, dilation, and segmentation of retinal vessels
  - Central and branch retinal vein occlusions
- Retinal vessels may also assume a yellowish tinge, also likely from anemia an leukocytosis

AML: Retinal findings (cont'd)

- Retinal **neovascularization is uncommon**
  - When seen, they are usually peripheral and have a sea fan appearance
- Peripheral **microaneurysms** are seen almost exclusively in **chronic leukemias**
  - Usually in CML with marked leukocytosis and thrombocytosis (WBC in range of a few hundred thousand)
  - Morse and McCready describe a CML pt with WBC in the range of 340,000 – 524,000 (23)

Morse PH, McCready JL: Peripheral retinal neovascularization in chronic myelogeous leukemia. Am J Ophthalmol 72:752-756, 1994

AML: other findings

- Vitreous involvement relatively rare given low rates of reporting in clinical and autopsy series
  - Likely due to ILM
  - Kincaid and Green report less than 1% of patients had vitreous involvement, but in the absence of massive retinal hemorrhage
- Choroid
  - Some series show the choroid, with its immense blood flow, is the most involved ocular tissue
  - Kincaid and Green show 65% had choroidal infiltration on autopsy, but this is rarely reported in clinical case series
    - Likely based on difficulty in clinical diagnosis of choroidal changes such as diffuse thickening
    - Overlying retinal findings easier to detect

Kincaid MC, Green WR, Kelley JS: *Acute ocular leukemia.* Am J Ophthalmology 112:372-379

AML: other findings (cont'd)

- Optic nerve
  - Involvement of optic nerve in leukemia is **rare**, clinically and histologically
  - Per Kincaid and Green, 3.6% had optic nerve involvement
  - Involvement of optic nerve predicts CNS infiltration and grim visual prognosis
  - Infiltration of optic nerve head or retrolaminar portion of optic nerve may appear clinically as pale gray swelling
    - Infiltration may be distinguished from disc swelling due to increased intracranial pressure
  - Early involvement may be associated with normal visual acuity
    - As infiltration progresses, irreversible visual loss may ensue
    - Therefore, early aggressive treatment is recommended, including radiotherapy with or without intrathecal chemo

Kincaid MC, Green WR, Kelley JS: *Acute ocular leukemia.* Am J Ophthalmology 112:372-379

AML: opportunistic infections

- Similar in presentation to complications from AIDS
- CMV retinitis most common disease in immunosuppressed patients, but other herpes viruses implicated
- In the setting of leukemia, ocular toxoplasmosis is the most common parasitic infection
  - These patients should be followed for reactivation and chemoprophylaxis given in those undergoing stem cell transplantation
- Disseminated fungal infections with ocular involvement is also seen
  - Candida most common pathogen

A case report

- Wasaki, et. Al describe a case of a 62 year old man with AML who developed an infiltrative optic neuropathy
- Patient had blurry vision OU for 2 years with optic disc edema in the right eye
- MRI showed swelling of the nerve and a right optic nerve mass with irregular enhancement of both optic nerves
- After chemoradiation, the vision improved
- Authors state "In this case, areas of enhancement within the optic nerve on MRI were very helpful in diagnosing the cause of visual loss and visual field defect in both eyes and optic disc edema in the right eye."

Wasaki, et al, *Infiltrative Optic Neuropathy in a Patient with Acute Myelogenous Leukemia*, Folia Ophthalmologica Japonica, Vol 50, No. 8, 671-675, 1999

AML: Ocular involvement treatment

- Ocular manifestations **usually not treated directly**
- Patients with ocular involvement but no evidence of CNS involvement are treated to those without CNS involvement
- See 'Treatment' section above
- Early empiric use of antifungal therapy decreased the likelihood of hematogenous spread of fungal infection to the eye
  - Our patient was treated with antifungals empirically based on his hematologic parameters
- In the Karesh study, all patients received induction chemotherapy
  - None received intrathecal chemotherapy or cranial or ocular irradiation
  - All ocular findings resolved in patients achieving complete remission and there was no residual visual deficit in any patient

Karesh, JW, Goldman, EJ, Reck, K, et al. A prospective ophthalmic evaluation of patients with acute myeloid leukemia: Correlation of ocular and hematologic findings. J Clin Oncol 1989; 7:1528.

Patient care, medical knowledge, practice-based learning, systems-based practice

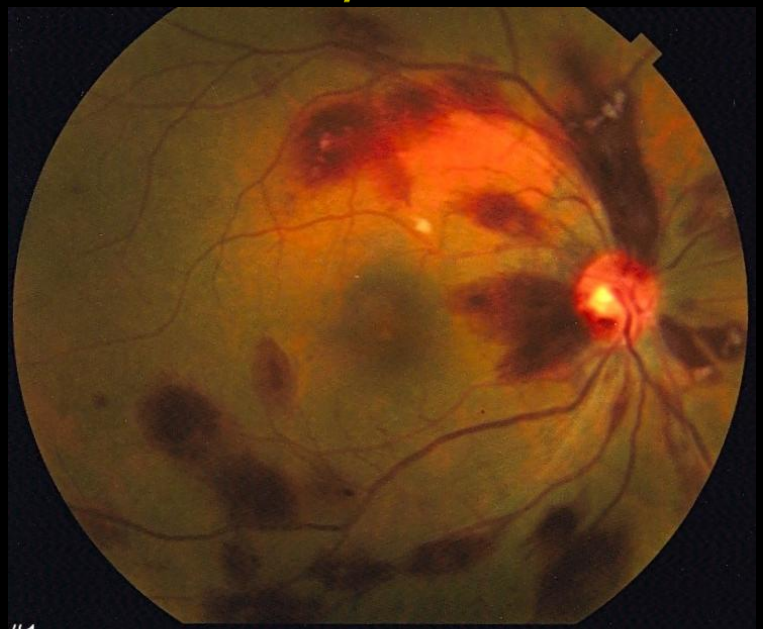
AML: Ocular involvement treatment (cont'd)

- Eye is a pharmacologic sanctuary so systemic chemotherapy may not reach it
- Rarely, local chemotherapy is used in treatment of ocular leukemia
- If optic nerve infiltration suspected, the posterior pole should be included in the radiation therapy portals for CNS prophylaxis
- More common in pediatric population with ALL

Back to our patient

- Further followup
- Patient returns to clinic on 10/27/10, 2 weeks after initial fundus photos
- Labs: **WBC 3.6 RBC 2.47, HGb 8.1, HCt 24.1, Plt 71**
- No change in visual acuity in either eye
- Fundus photos show some interval improvement in retinal and vitreous hemorrhage (see photos)

10/13



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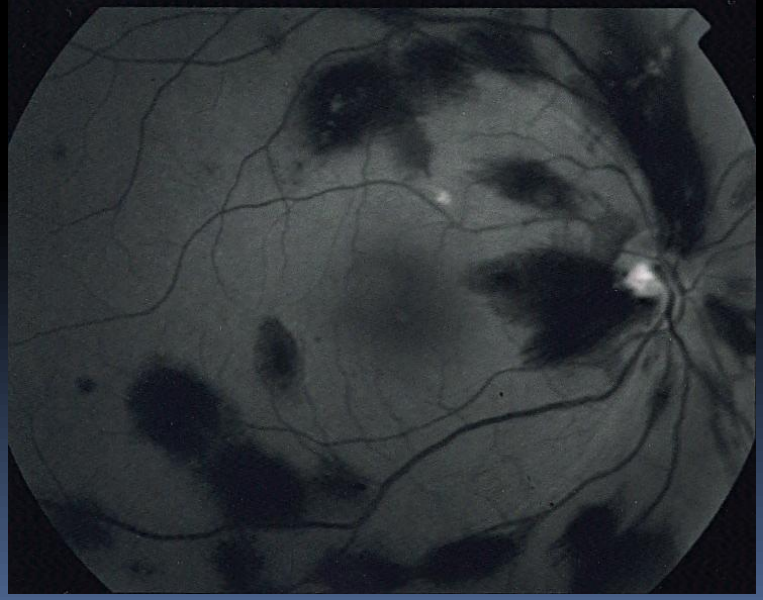

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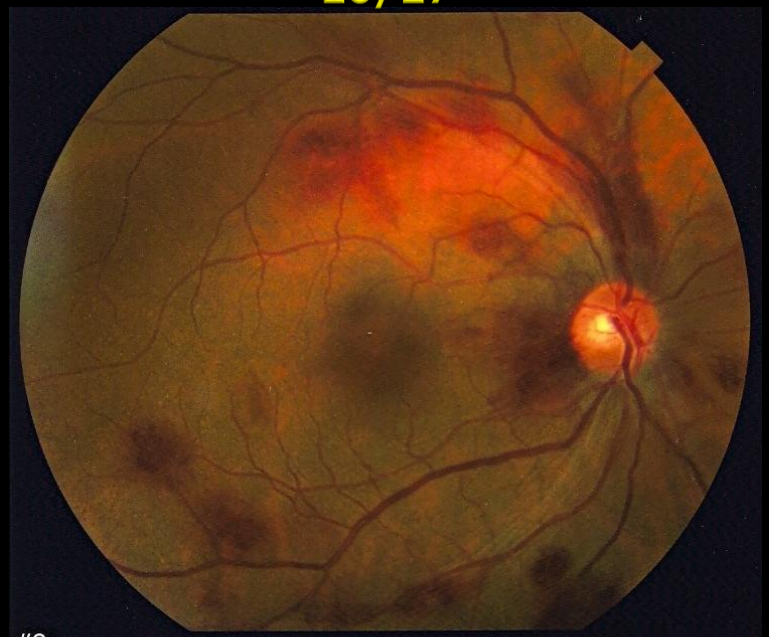

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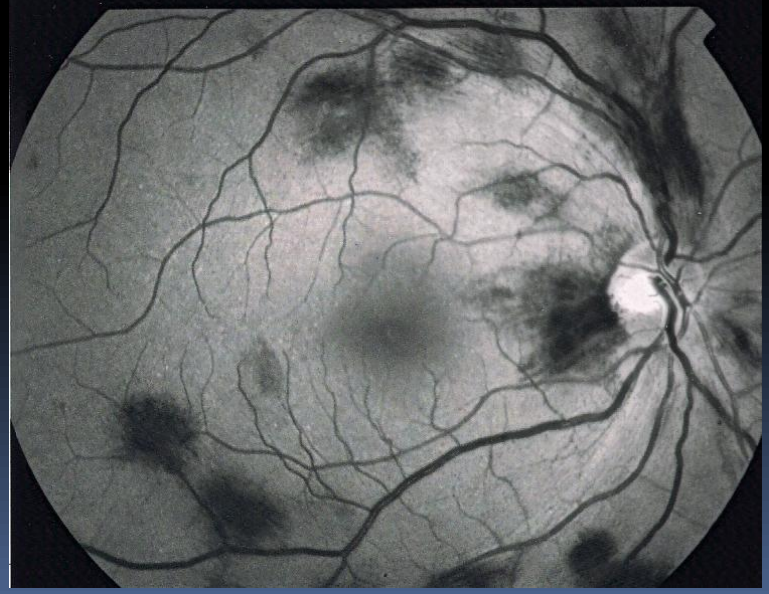
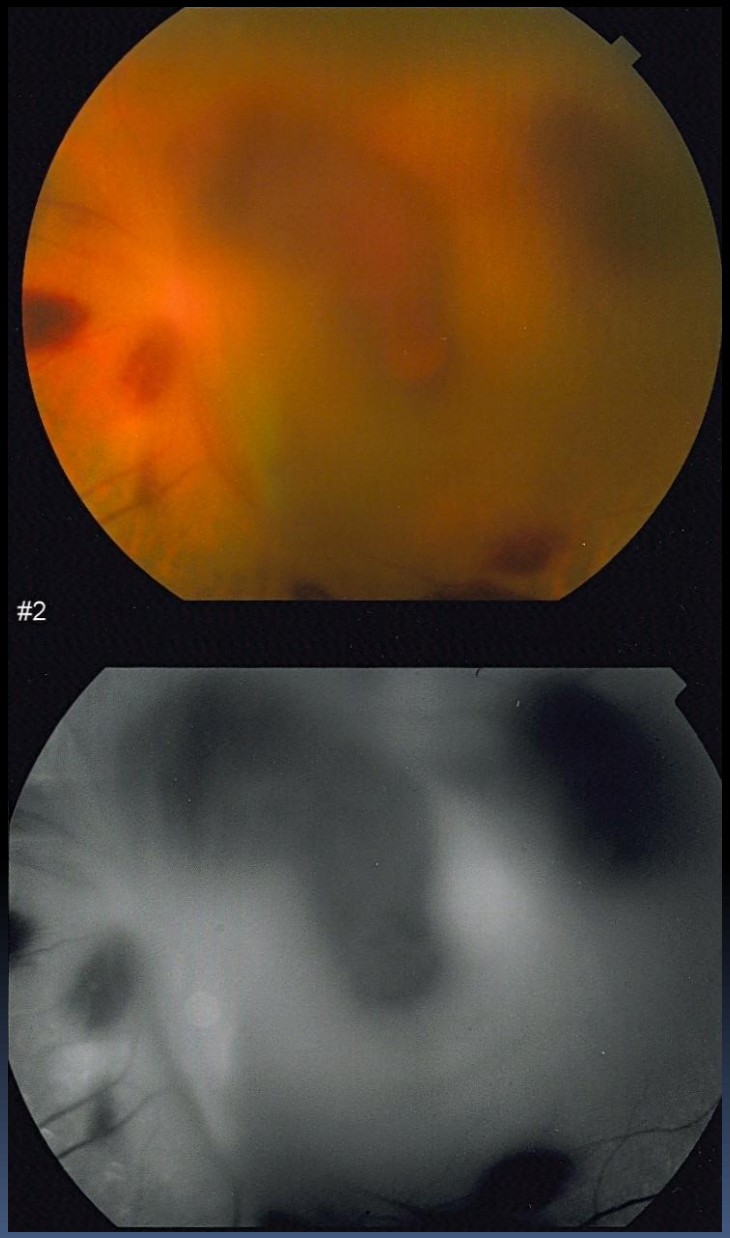


Patient care, medical knowledge, communication

10/13



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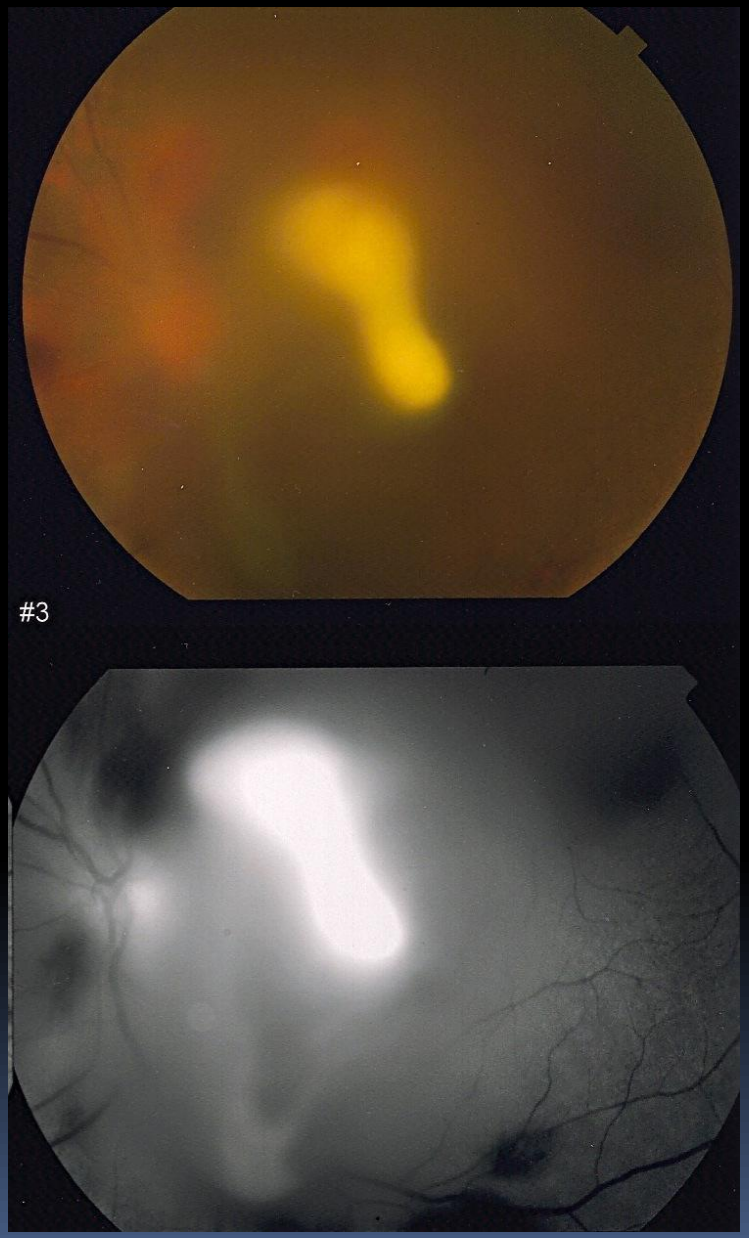

Patient care, medical knowledge, communication

Even Further Followup

- Pt seen at bedside on 11/17/10
- NVa OD unchanged, OS: 20/200- ph 20/100+
- P: 3-2 no APD OU
- Labs: **WBC 2.6 RBC 2.96, HGb 9.4, HCt 26.5, Plt 27**

Core Competencies

- **Patient Care**
  - Description of the case and management of the patient
- **Medical Knowledge**
  - Evidence-based medicine applied to this patient's care
- **Interpersonal and Communication Skills**
  - Explaining to the patient the basis for their condition and their prognosis, communicating with other medical specialties
- **Professionalism**
  - Timely patient work up
- **Practiced-Based Leaning and Improvement**
  - Evidence based medicine applied to the patient's care
- **Systems based practice**
  - Coordination of care between multiple specialties

Reflective Practice

- I feel that the care of the patient was adequate and performed in a timely manner, care was co-managed with various medical disciplines, there was good communication with these specialties and with the patient and there were no delays to diagnosis and appropriate treatment.

Acknowlegement

- Dr. Edelstein
- Dr. Gombos
- Dr. Greenberg
- Dr. Enriquez
- Our patient

Thank You

Questions?

References:

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