Learning from Error

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Learning from tragedy: the Julia Berg story

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Abstract: This is a case report involving diagnostic errors that resulted in the death of a 15-year-old girl, and commentaries on the case from her parents and involved providers. Julia Berg presented with fatigue, fevers, sore throat and right sided flank pain. Based on a computed tomography (CT) scan that identified an abnormal-appearing gall bladder, and markedly elevated bilirubin and "liver function tests", she was hospitalized and ultimately underwent surgery for suspected cholecystitis and/or cholangitis. Julia died of unexplained post-operative complications. Her autopsy, and additional testing, suggested that the correct diagnosis was Epstein-Barr virus infection with acalculous cholecystitis. The correct diagnosis might have been considered had more attention been paid to her presenting symptoms, and a striking degree of lymphocytosis that was repeatedly demonstrated. The case illustrates how cognitive "biases" can contribute to harm from diagnostic error. The case has profoundly impacted the involved healthcare organization, and Julia's parents have become leaders in helping advance awareness and education about diagnostic error and its prevention.

Keywords: diagnostic error; Epstein-Barr viral infection.

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Introduction

Medical errors have been implicated as the third leading cause of death in the US [1], and diagnostic errors account for many of these [2, 3]. Diagnostic errors result from complex interactions between health care systems, providers and patients and are almost always caused by multiple factors. Previous studies have shown that most diagnostic errors result from a combination of systems and cognitive factors, often resulting in patient harm.

One of the most important responses when diagnostic errors occur is to formally analyze cases to determine why the error occurred and implement effective feedback for providers and systems to avoid similar errors in the future. This is the key to developing expertise for providers and is a nearly universal desire of patients and their families who have been harmed by diagnostic error. Here we share the story of Julia Berg, the diagnostic error that contributed to her death, and how providers, learners and systems continue to learn from Julia's story.

Case presentation

Clinical course

Julia was a 15-year-old previously healthy girl who presented to urgent care with 1 week of fevers, fatigue and a sore throat. She developed a prolonged nosebleed, which was unusual for her, prompting her parents to bring her in to the urgent care clinic. In the clinic, she was found to have leukocytosis (11.8 K/mm^3) with 76% lymphocytes and 9% monocytes as well as thrombocytopenia; a blood smear showed reactive lymphocytes. Urinalysis was notable for large leukocyte esterase, bilirubin and urobilinogen, 10–20 WBC/HPF, 5–10 RBC/HPF, 'many' bacteria with few squamous cells and no casts. The presumptive diagnosis was a urinary tract infection, and a culture subsequently grew >100,000/mL pan-sensitive *Escherichia coli*. She was started on oral cephalexin. Two days later, she was seen for follow-up in her pediatrician's office by one of the pediatrician's partners whom she had never seen before. She had fever to 102°F (38.8°C) with

chills, headache, abdominal cramps and another nosebleed, along with being "very tired" but denied dysuria. She had been encouraged to drink extra fluids but could not because of a sore throat. She also complained of sharp right upper quadrant abdominal and flank pain that was rated 7–9/10 in intensity, and worse on palpation during inspiration. There was also left upper quadrant abdominal pain and tenderness of lesser intensity. A repeat complete blood count (CBC) showed 79,000 platelets/mm^3, and 18,100 WBC/mm^3 with 79% lymphocytes. The impression at this follow-up visit was a possibly resistant bacterial urinary tract infection. She was given ceftriaxone 2 g intramuscularly and started on oral ciprofloxacin.

She was seen again 2 days later (now 11 days after the onset of her illness) in her pediatrician's office. Her fevers had abated, and her appetite had improved, but she continued to have right-sided flank pain with tenderness with palpation at the costovertebral angle. An urgent computed tomography (CT) scan was ordered to exclude a perinephric abscess that showed no evidence of abscess or pyelonephritis but the right ureter appeared minimally dilated. The liver was normal in size and homogenous in appearance. The gallbladder appeared markedly abnormal with thickened walls and pericholecystic fluid. The spleen was "upper limits of normal" in size. The radiologist's impression of the CT was recorded as: "cholecystitis and diseases which can affect the gallbladder secondarily such as with hepatitis". A repeat urine culture was sterile after 24 h.

She was admitted electively to a tertiary children's hospital for suspected cholecystitis and evaluation for other possible diagnostic considerations, such as pancreatitis, choledocholithiasis and nephrolithiasis.

On admission she was again febrile (38.8°C). Labs were notable for elevated bilirubin (7.2 mg/dL), predominantly conjugated (5.2 mg/dL) with elevated aminotransferases (see Table 1). Amylase and lipase were normal. Her CBC continued to reveal marked lymphocytosis, although this was not commented upon in the admission notes.

An abdominal ultrasound noted a positive sonographic Murphy's sign [increased right upper quadrant (RUQ) pain with palpation] and marked thickening of the gallbladder wall. The common bile duct was normal in size. There was no suggestion of cholelithiasis or choledocholithiasis, "although the marked increase in echogenicity of the wall as well as the minimal intraluminal fluid makes it difficult to definitively exclude the presence of a small stone". The liver and intrahepatic biliary tree were otherwise normal. The impression was "consistent with cholecystitis". She was started on IV piperacillin/tazobactam and a surgical consultation obtained. The surgery team reviewed the CT and ultrasound findings and concluded that Julia had hyperbilirubinemia and fever, consistent with cholecystitis and possible biliary obstruction.

A pediatric gastroenterology consultation on the second hospital day noted the abnormal liver function tests (LFTs) and imaging studies, but again did not mention the hematologic abnormalities. Their impression was cholecystitis without ductal dilation, although the "elevated direct bilirubin was concerning". The consultant stated they "…would not search for alternative etiology for increased labs as they can be explained by cholecystitis". The plan was to repeat imaging if the bilirubin increased and consider an endoscopic retrograde

Table 1: Laboratory results – Julia Berg.

Normal range		5-Aug	6-Aug	7-Aug	8-Aug	9-Aug	10-Aug	
							Pre-op	Post-op
0.2–1 mg/dL	Bili	7.2	7	6.7	7.6		9.6	
0.0–0.3 mg/dL	Direct bili	5.2	5.3	5.2	5.7		7.3	
3.5–4.9 g/dL	Alb		2.5	2.1			2	
42–168 U/L	Alk Phos	393	431	451	561	604	659	
30–65 U/L	ALT	249	184	161	161	180	179	
23–60 U/L	AST	189	132	130	163	209	211	
20–210 U/L	Gamma GT		290	271	280			
114–286 U/L	Lipase		406	320	321	383	80	
20–110 U/L	Amylase	39	85	59	46	45	102	
12–16 g/dL	Hgb		11.9	12.2	12.7	12.3	11.4	5.8
150–450 K/μL	Plts		134	134	151	157	147	
4.5–11.3 K/μL	WBC		25	28*	39.9*	47*	43.8	
25–45%	% Lymphs		86%	93%	94%	94%	92%	

*WBC values phoned to ward and read back by nurses Aug 7–9.

cholangiopancreaticogram (ERCP). The surgical consultant concurred with the impressions of cholecystitis and possible cholangitis.

Over the next 2 days, she remined febrile to 38.9°C and continued to have marked RUQ tenderness to palpation, although her appetite and oral intake improved. Her aminotransferases and bilirubin were again noted to be elevated but her persistent lymphocytosis was not commented upon in the progress notes. Given her lack of definitive improvement, a hepatobiliary (HIDA) scan was performed on the fifth hospital day that revealed: "Excellent hepatic extraction of isotope is seen. At no time is there visualization of the GB or activity in the intestinal tract".

The next day, pediatric and surgery continued to note the persistent elevations of LFTs without mentioning the CBC abnormalities. An ERCP was performed that revealed no stones and normal biliary flow. *The endoscopist made a prescient comment: "Have we found unifying diagnosis?"*

On the seventh hospital day, now over 2 weeks into Julia's illness, the surgical consultant documented a discussion including the surgeon and both gastroenterology (GI) consultants (the consultant and physician who performed the ERCP). The decision was made to proceed with a laparoscopic cholecystectomy with a liver biopsy. A GI note notes the ERCP findings and persistently elevated bilirubin and LFTs. The pre-operative platelet count was 147 K/mm^3.

Julia was taken to the operating room for a laparoscopic cholecystectomy and liver biopsy. Anesthetic agents and adjunctive medications included fentanyl, midazolam, rocuronium, lidocaine, propofol and ondansetron. At the initiation of the surgical procedure, a nasogastric tube was passed with return of a small amount of blood. This cleared immediately, but one unit of fresh frozen plasma was ordered and transfused. The laparoscopic procedure was uneventful with minimal (10 mL) blood loss. The surgical field and biopsy site were noted to have achieved hemostasis before surgical closure. The surgeon's dictated postoperative note mentions gallstones demonstrated on one of the pre-operative imaging exams, in conflict with the imaging reports which specifically report the absence of visible stones.

Approximately 2 h post-operatively Julia became hypotensive, hypoxic, unresponsive and a "code blue" was called. A blood gas revealed a pH of 7.14, with a pO_2 of 90 mmHg and pCO_2 of 58 mmHg. A repeat pH was <6.8. A serum calcium was grossly elevated; serum potassium was >10 mEq/L. Hemoglobin (Hgb) was 7.5 g/dL (compared to 11.3 g/dL pre-op); on repeat, the Hgb was 5.8 g/dL. She was given fresh frozen plasma, packed red blood cells and crystalloids. Aggressive cardiac resuscitation did not achieve return of spontaneous circulation, and Julia was pronounced dead 1 h later.

Autopsy

Gross findings were notable for petechiae of the skin and palette, blood in the GI tract with no single source of bleeding, and adrenal medullary hemorrhage, all thought to reflect disseminated intravascular coagulation (DIC). The liver was enlarged (2100 g) and showed chronic hepatitis with focal areas of endothelial inflammation, predominantly with lymphocytes, and mild cholestasis. Immunohistochemical stains revealed a T cell (CD3 positive) predominant inflammatory infiltrate with only scattered B cells (CD20 positive) and no terminal deoxynucleotidyl transferase (Tdt) positive cells that would have suggested a lymphocytic malignancy. In situ hybridization for Epstein-Barr virus (EBV) showed a moderate number of positive cells. The gall bladder showed a chronic inflammatory infiltrate, similar to that seen in the liver, with no evidence of gallstones.

Post-mortem blood tests found elevated levels of EBV IgM antibody (50 AU, normal 0–19) and negative antibody screens for cytomegalovirus, and hepatitis B and C. IgG antibodies to hepatitis A were elevated but there were normal levels of anti-Hep A IgM.

The autopsy diagnosis was active EBV infection with moderately severe hepatitis and DIC, citing this as an unusual but well-described complication of EBV infection [4].

The discharge coding included all of the procedures and various diagnoses including cholecystitis and choledocholithiasis, but no mention of EBV infection. Her death certificate listed the cause of death as "Complications of disseminated intravascular coagulation and liver failure" and "Fulminant Epstein-Barr virus infection".

The parent's perspective (Dan Berg and Welcome Jerde)

We were visiting friends west of Minneapolis when our daughter Hannah called about her sister's nosebleed. Hannah was 12; Julia was 15. The normal remedies hadn't worked, and there was a bit of panic in her voice. We coached her through some alternative strategies and began the 40-minute drive home.

That evening, the nosebleed was under control, but her mother, Welcome, took Julia to urgent care. This wasn't

a normal nosebleed and she hadn't felt well all week, with fatigue, a sore throat, and sometimes a low-grade fever.

After a 90-minute wait, the physician on duty determined from a urine sample that Julia had a kidney infection. As they prepared to leave the office with a prescription for an antibiotic, the doctor asked Welcome, "Does Julia look normal to you?" "Well, more or less, yes." "Huh", he said. "My first thought was that she might have leukemia".

That was a Sunday. By Tuesday, Julia wasn't getting better so Welcome took her to our pediatrician's office. The antibiotic was changed, and we agreed to stop back on Thursday for a final checkup before a long-planned vacation.

By Thursday, Julia said she felt better and was eager to put this behind her and hit the road. As she rose from the exam table the pediatrician noticed a wince. Probing, it seemed her right side was still pretty tender.

The doctor thought we should go to Minneapolis Children's Hospital for a CT scan, just to make sure there wasn't something else going on. Following the scan, the doctor said that Julia didn't have a kidney problem. Great news! But…she had a gall bladder infection. Gall bladder? In a fit, slender 15-year-old? Unusual, but not unheard of, we were told. We were persuaded that Julia should be admitted for further assessment and possible surgery.

Over the next 5 days, and a parade of attendings, residents and specialists, we learned that Julia's platelets were low and that her liver tests were abnormal. We heard from one doctor that she didn't appear to have any gall stones; but, according to another, she had lots, but they were small. More than once, someone looked at her chart, and said "weird". She was scheduled for surgery. Then she wasn't. There were a series of tests, but all were taken with the assumption that the gall bladder needed to be removed.

Her platelets stabilized, and surgery was finally scheduled for Wednesday morning. But, as a final check on Tuesday night, she was transported to the adjacent adult hospital for an ERCP, a special type of endoscopy to visualize the bile drainage system. The gastroenterologist sat down with us following the procedure. He was puzzled. There didn't appear to be any obstructions or stones. He had performed a sphincterotomy, just in case. The results weren't as expected, he wasn't sure of the diagnosis, and he wasn't sure Julia should have surgery. He said he would have a conversation with the surgeon in the morning to discuss his observations. Julia went back to her room and we went home. Our sleep was fitful; but, we reminded ourselves that we were at a great hospital with great physicians.

We were back at the hospital at 6:30 a.m., uncertain whether surgery would happen. By late morning it was scheduled, but it wasn't until we were outside the operating room, that the surgeon confirmed that he had spoken with the gastroenterologist. They agreed that he would proceed with the cholecystectomy and do a liver biopsy to rule out other contributing factors.

Julia was a bit lightheaded as she was prepared for surgery. We met with the anesthesiologist. Consent forms were signed. We kissed our daughter and assured her that everything would be okay.

After 90 minutes the surgeon called us from the waiting room. He said the procedure had been successful and without complications. They had removed the gall bladder laparoscopically, as planned, and taken the liver biopsy. The resident surgeon would complete the procedure and let us know when Julia was in post-op. After another half hour, the resident reported in as promised. Everything looked fine, although Julia had received a unit of blood during surgery, and her hemoglobin was unusually low. Additional blood and fresh-frozen plasma had been ordered as a precaution. They would let us know when she was ready to return to her room.

Eventually Julia was the only one left in post-op, so we could enter and visit. She was talking with the nurse about the movie that she had watched that morning. Apart from a dark stool post-surgery, everything seemed under control. The post-op nurse spoke with the charge nurse on Julia's non-surgical floor and was assured that she would monitor Julia's status. The expected blood and FFP would be forwarded to her room on the sixth floor. We accompanied her to her room, where she could rest and recover. Dan went home to pick up Hannah for a post-surgery visit. It was 3 pm.

Welcome stayed with Julia and assisted the nurse in turning Julia as she passed another bloody stool. Once the bed was cleaned, there was another bloody stool. Julia was in pain and asked for more pain medication. Welcome noticed that when mentioning the pain, Julia pointed to her chest, not the surgical site. Welcome repeatedly asked when the blood and FFP would arrive. She was told it would be there by 4:00. At about 3:40, Dan checked in by phone. Welcome sensed that things were going wrong asked him to come back immediately.

Welcome noted that on the monitors Julia's blood pressure was dropping and heart rate increasing. The nurse dismissed her concern and continued to focus on cleaning up the bed. Welcome continued to watch the monitor in dismay as Julia's BP and heart rate continued to spin out of control. At Julia's side she attempted to comfort her…"it will be okay, Honey." Then, in her mother's arms, Julia's eyes rolled back. The code team descended and tried but failed to save Julia. Ninety minutes later, the surgeon, who

had left the hospital after completing the surgery and was called back, delivered the news to Welcome and Dan.

After Julia died

Within 10 days following Julia's death, the hospital CEO and CMO initiated a meeting to apologize, discuss what had gone wrong, and explain the changes in procedures and practices that they adopted as a response to our tragedy. Six weeks later, at our request, the hospital's CMO arranged a meeting for us with six members of Julia's medical team and the CEO. They answered our questions, and acknowledged how they and the system, had failed. The gathering was not confrontational in any way. We were grateful for their self-reflection and candor.

In 2007, 2 years after Julia died, we settled a wrongful death lawsuit with the hospital and the doctors. It was a painful process for us, but we felt that we needed an independent assessment of what happened, and the legal system provides for this. At every turn we encountered nothing but respect and compassion from the hospital leadership.

Following the settlement, the hospital leadership again requested a meeting to provide an update on the changes implemented since Julia's death. We were told that a day rarely goes by at the hospital without a reference to Julia or a recollection of her case.

The introduction of a "Rapid Response" program was accelerated and launched soon after Julia died. The admissions process for new patients included specific instructions (printed in four languages) to parents about this program and how to initiate a request regarding the condition of their child. There were several other changes and actions taken that were directly related to Julia's case. Many of these have become standards of care nationally in the decade since our loss.

Every hospital knows tragedy, but Julia's case was special. We know that the trauma rippled throughout the hospital and to the broader medical community. We take some comfort in learning of the changes in policy and practice that have been adopted by the hospital. Her death inspired and accelerated significant changes, and her case is being used to promote patient safety reforms well beyond our community.

Family's reflection

How could we, Julia's parents, have prevented this outcome? We are haunted by this question [5]. We can't undo what has been done; we can't bring Julia back. We believe our best option is to share Julia's story and advocate for changes in the systems and culture of medical care. We focus much of our attention on the engagement of patients and families in the diagnostic process. Providers must do a better job of empowering patients and families as partners and participants in developing a diagnosis and treatment plan. The medical team may have great knowledge and technology at their disposal, but the patient and the patient's family are the experts on the person at the center of this medical encounter.

Until all physicians are deliberate and rigorous in creating differential diagnoses in every situation, health care consumers need to be vigilant and assertive, willing to challenge the narrative that is being developed about their loved one. This will not happen naturally for many people. There are cultural and traditional norms of respect and trust that inhibit patients and families, which is why we focus on the institutional responsibility of providers to actively invite dialog. Acknowledging uncertainty – even if it is slight – can engage the patient and perhaps elicit additional history and a revision of the differential diagnosis.

We felt that we were knowledgeable and assertive advocates for Julia but, for the most part, we were seen by the medical team as "interested observers". As the case presentation shows, there were many opportunities to "stop the line" and reassess. We didn't fail Julia. The system did.

Perspective of the hospital: Philip Kibort

There are certain events in a clinician's life that are never forgotten. The death of one's patient seldom doesn't cause some amount of angst, self-reflection, questioning of competency and raises moral as well as ethical questions. In the management of healthcare, tragic events are also major emotional episodes that are seldom forgotten.

Julia's death was a watershed tragedy for our hospital and a significant, if not quote "the event" that changed me personally and professionally, as a clinician and as an administrator.

In 1999 my Children's Hospital began its journey to wanting to become one of the safest if not the safest children's hospitals in the United States or North America. Our CEO after being told to withhold information from a family whose son died of an abnormal and poor diagnosis met with the family and basically didn't tell them the

truth. He came out of that meeting vowing never to do that again and to become a company and hospital that would be fully transparent from that point on. He went on to hire a new chief operating officer who had great expertise in patient safety and it was she who changed our culture. One of the main tenants of the organization's cultural change was to be fully transparent with all families whenever a medical error occurred.

One of my responsibilities as chief medical officer was to be the person from administration who would meet with the families to apologize when an error that we created caused harm to their child. It was the most difficult part of my job, but one that was the right thing to do. Our commitment as an organization was always to tell the family right away what we knew.

Julia's death impacted me as a physician and as Chief Medical Officer. It was the first time in my 30-year career in medicine that I realized and understood that a cognitive "bias" caused the death of a patient under my responsibility. It was immediately after her unfortunate death that I became interested and committed to personally learn and understand the impact of cognitive biases on diagnostic errors. At the same time as CMO it became my goal and commitment to begin changing the culture of both our medical and clinical staff to understand how our cognitive biases are potentially hurting our pediatric patients. In addition, because of the Bergs' willingness to work with us at Children's Minnesota we were able to use Julia's story multiple times over the years as a teaching opportunity for all our staff and trainees.

Julia's death changed me drastically as a physician and as an administrator. Julia's parents, because of their unbelievable resiliency, kindness and compassion, allowed themselves, myself, and our Children's Hospital to heal together after her death.

Discussion

This case involved a fatal diagnostic error: a previously-healthy 15-year-old girl was diagnosed with cholangitis and suspected biliary obstruction, whereas the autopsy-confirmed diagnosis was something completely different – active EBV infection (mononucleosis).

Although other causative factors almost certainly contributed, the most notable factor in this case is that none of the providers seemed to have noticed or considered the importance of the patient's lymphocytosis. Atypical lymphocytes are the hallmark of mononucleosis and the disease owes its name to this key manifestation [6]. None of the medicine, surgical or gastroenterology notes commented on either the leukocytosis, the marked lymphocytosis, or the atypical cells. On 3 days, there are notes in the laboratory results section documenting that the elevated white blood cell count was called up to the ward and reported to nursing staff. A question remains as to whether informing nursing staff by the laboratory personnel is sufficient to meet the requirement of informing a responsible care provider of a result. Nursing staff, especially those who are on general surgery floors, may not have been conversant with abnormal hematology results. They may have focused only on the elevated white blood count, a common enough finding in the setting of infectious conditions including cholecystitis. Whether laboratory staff highlighted the more unusual and critical finding of lymphocytosis and in particular the presence of atypical lymphocytes is not known. There is no documentation as to whether the physicians were ever informed, either by the laboratory staff or nursing staff, or if they were, their thoughts on this. Another potential causative factor may be the quality of laboratory report itself. Traditional laboratory reports list numeric values (e.g. hemoglobin 12.2) or short descriptors (80% lymphocytes) with control values. Interpretive results are limited to a small number of circumstances. An interpretive result, where the report said, "atypical lymphocytosis – this finding is commonly seen in the setting of viral infections, most commonly infectious mononucleosis", may have triggered a different response from the patient's care providers.

Mononucleosis classically presents with sore throat, fevers and a profound sense of fatigue, especially in teenagers and young adults. All of these symptoms were noted in the ambulatory care visits but were downplayed or lost completely when Julia was admitted to the hospital; the inpatient diagnostic efforts were re-directed to understand her cholestasis and direct hyperbilirubinemia. Acalculous cholecystitis is a rare presentation of Epstein-Barr infection, and though now well documented in the medical literature [7–14], was not considered by any of the clinicians ante-mortem. Further, the initial reading of the ultrasound mentioned that the gallbladder abnormalities could have been secondary to another, possibly hepatic process.

Based on the combined findings of fever, right-upper quadrant pain and tenderness, and markedly abnormal bilirubin and LFTs, Julia was thought to have obstructive biliary disease requiring surgical intervention. Surgical intervention would have been clearly indicated if stones had been documented and the patient was clinically deteriorating, but neither of these were present. It is possible, given the surgeon's note, that they mistakenly believed Julia did have gallstones, but one then wonders why this

was not aired at the conference with the gastroenterologist pre-operatively.

What was the fatal post-operative event and what triggered this?

Fatal cases of Epstein-Barr infection are vanishingly rare, with the possible exception of infections (sometimes chronic) in immunocompromised patients. In our view, the etiology of the sudden, profound fatal post-operative event in Julia's case remains incompletely explained. DIC has been described in EBV infection [4, 15], and could explain the catastrophic collapse, but the classical findings at autopsy, namely diffuse microthrombotic lesions [16], were not identified. Finding microthrombi, however, is highly dependent on performing a detailed and concerted microscopic search. A second possibility, suggested by the dramatic fall in Julia's hemoglobin concentration from 11 g/dL pre-operatively to 5 g/dL during the "code", is acute intravascular hemolysis. Acute hemolytic reactions, another unusual complication of EBV infection, have been described repeatedly in the medical literature [17–20]. In most cases, this has been associated with cold hemagglutinins [21, 22]. Surgery has been associated with acute hemolytic reactions in the presence of cold agglutinins, especially in the setting of extracorporeal circulation [22, 23]. Alternatively, the fatal event could have been triggered by one of the anesthetic agents, the intra-operative transfusion, or some other as-yet-unidentified factor.

The autopsy did not clearly identify the immediate cause of death. Because it was a sudden and unexpected death, the autopsy was performed at the medical examiner's office and this likely limited the iterative communications between care-providers and the medical examiner to fully identify the sequence of events that lead to the patient's demise. A clinico-pathological discussion conference, where the autopsy results are reviewed in the context of the clinical history, probably did not happen. In retrospect, some possible explanations for the sudden cardiovascular collapse that should perhaps have been considered/explored include myocarditis and hemophagocytic lymphohistiocytosis [24–26], both of which have been associated with death, including occasional sudden death, in EBV infection. The examination of the heart is reported to have lymphocytosis, but more extensive assessment to define extent and severity are not reported. Similarly, the examination of various tissues, including the bone marrow does not specifically list the exclusion of hemophagocytosis, which might have been better defined by using special stains. In addition, the cancelation of blood tests after the demise of the patient limit definitive diagnosis of hemophagocytic lymphohistiocytosis (e.g. assessment of ferritin levels, and sCD25 levels).

Regardless of what the trigger was for the sudden collapse, it seems to have been related to the surgical procedure, which almost certainly would have been avoided if the working diagnosis had been mononucleosis instead of obstructive biliary disease. Medical management, primarily of a supportive nature, has generally been the preferred treatment in previous cases of EBV-associated acalculous cholecystitis.

Trying to understand the diagnostic error

When analyzing diagnostic errors, it is fundamental to use a standard approach that seeks to delve systematically into the error's causative factors and minimizes bias. In other areas of patient safety, this has been accomplished through the use of a "fishbone" diagram that categorizes causative factors that, in combination, lead to the error as an outcome. This approach has been successfully adapted to analyze diagnostic errors [27]. Figure 1 uses a modified fishbone to designate some of the causative factors for the diagnostic error in Julia's case. The diagram illustrates the many different potential sources of error in this case and also the complexity of the diagnostic process.

The National Academy of Medicine described diagnosis as a process and most diagnostic errors involve some breakdown in one or more steps of this process [2, 28]. The key failing in this case lies squarely in failing to appreciate salient laboratory data; Julia's atypical lymphocytosis was the clue to unlocking the correct diagnosis. Closer attention to the history might also have triggered consideration of a viral illness, given the complaints of sore throat, fever and prominent fatigue. Further, it appears that the providers focused entirely on the biliary tract without stepping back to ask, "What causes fever, sore throat, lymphocytosis and thrombocytopenia in a teenager?"

Cognitive shortcomings can be identified retrospectively in most cases of diagnostic error [29]. Problems that could have conceivably contributed to the diagnostic error in the case of Julia Berg included:

– Framing and context errors – from the moment of admission, the suggested diagnosis was cholecystitis, most likely due to gallstones. Framing the case as being a "GI" problem may have discouraged reconsidering it in an infectious disease context.

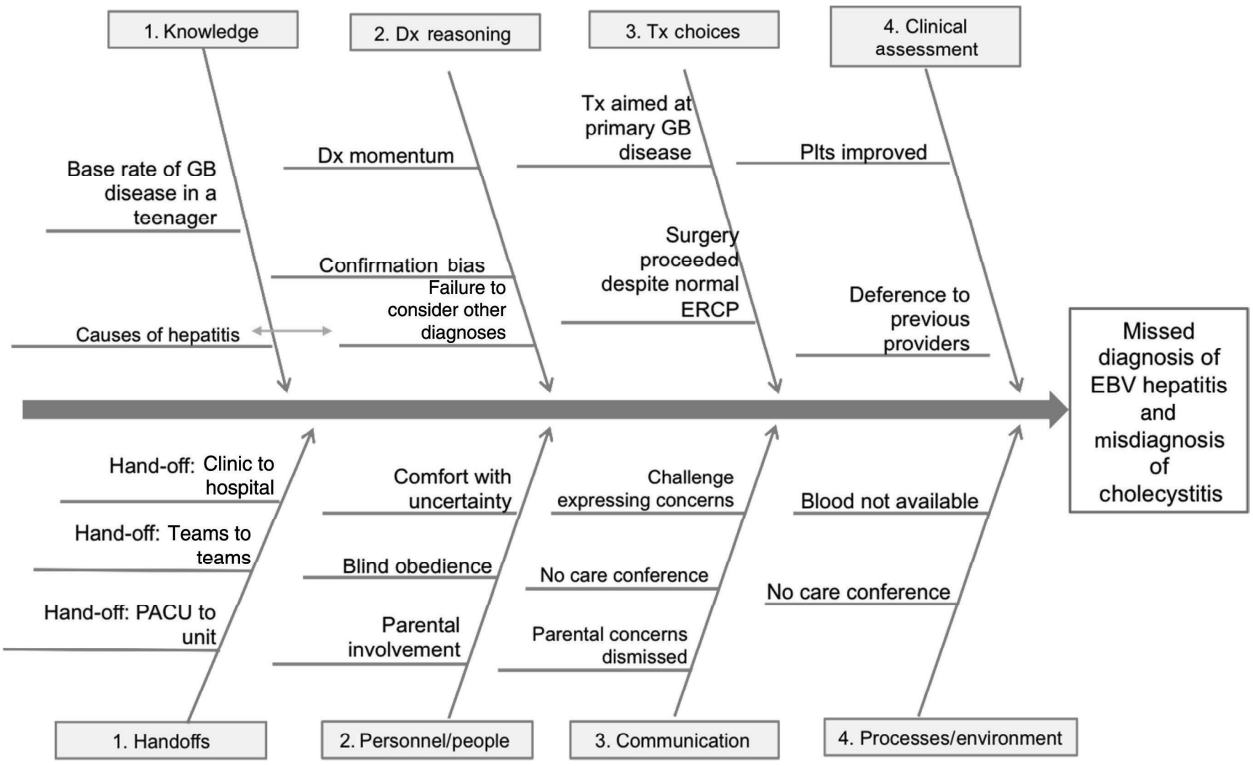

Figure 1: A fishbone diagram illustrating factors that might have contributed to the diagnostic error, missing the diagnosis of EB virus infection.

- Diagnostic momentum – findings that could have led to a different diagnosis were discounted, if not completely ignored (not volitionally).
- Premature closure – because it explained many features of the case, the diagnosis of acalculous cholecystitis was plausible, and no other entities were seriously mentioned. An assigned diagnosis tends to stop further thinking. Was a comprehensive differential diagnosis constructed at any point? In a study by Singh and colleagues of diagnostic error cases, there was no documentation of the differential diagnosis 80% of the time [30]. Similarly, premature closure may have contributed to a curtailed autopsy. Because the "proximate" cause of death (in pathology, that which in natural and continuous sequence led to the series of events that eventually resulted in the patient's demise) – EBV infection – was discovered early, efforts to identify the "immediate" cause of death, the sudden cardiovascular collapse, were not considered, explorations that often requires detailed biochemical, hematologic and microscopic assessments.

Similarly, system factors can be identified in most cases of diagnostic error, and there were several such factors to consider in this case:

- Residency supervision: there are only a few notes by the medical, GI and surgical attendings. Would closer supervision have made a difference?
- Decision support: many effective and easy-to-use web-based tools are available to assist with differential diagnosis. Were these available?
- Test result communication: the ward staff were notified of Julia's highly abnormal white cell count on at least three occasions. Were the results communicated to the appropriate decision maker with respect to diagnostic responsibility? Is it reasonable to deliver results and receive results of some urgency by non-diagnostic care providers? Were the results ever communicated and acknowledged by the physician staff?
- Laboratory involvement: was the laboratory pathologist consulted about the meaning of the "abnormal lab finding"? Was anyone in the lab curious about such extreme lymphocytosis in a non-cancer patient? Should the lab report have included a note that said "atypical lymphocytes in a teenager is most commonly associated with EBV infection"?
- Multidisciplinary huddle/discussion: multidisciplinary discussions (tumor boards) are common for cancer diagnosis, where specialty expertise needs to come together in the context of the whole. A parallel

process, allowing communication with pathologists, hematologists, surgeons, the ward team and the family may have helped paint a complete picture.

The case also prominently brings to attention how the family and caregivers can contribute to patient safety. Julia's mother noticed Julia's progressive deterioration in the recovery room, but her observations were dismissed by the staff. It is impossible to know if a more receptive response would have made a difference. Acknowledging the voice of the patient and the family is now thought to be one of the most powerful interventions available to improve safety, by creating a new safety net to catch deterioration and errors. Accordingly, many hospitals now encourage patients and families to participate in "rapid response" programs [31], and the efforts of the Children's Hospital to promote patient engagement are exemplary.

In summary, the death of Julia Berg illustrates the multifactorial origins of diagnostic error and identifies many opportunities for improving the diagnostic process going forward. The case provides lessons for providers and healthcare systems. This feedback is vital, so that when errors occur, we can promise families that "We are doing everything humanly possible to learn from this case so this never happens again".

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