GAVIN PUBLISHERS

Archives of Pediatrics

Apsel Winger B. Arch Pediatr: JPED-140.

DOI: 10.29011/2575-825X. 100040

Case Report

Pediatric Malignancy Manifesting as Serious Infection

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Citation: Apsel Winger B, Weintrub P (2017) Pediatric Malignancy Manifesting as Serious Infection. Arch Pediatr: JPED-140. DOI: 10.29011/2575-825X. 100040

Received Date: 09 December, 2017; **Accepted Date:** 22 December, 2017; **Published Date:** 02 January, 2018

Abstract

Pediatric hematological malignancies and infection share many presenting symptoms. When infection is the initial manifestation of malignancy, it can delay the malignancy diagnosis. We report four patients who presented with severe infections: ecthyma gangrenosum, osteomyelitis, sepsis, and thrombophlebitis. Persistent abnormal clinical features led to bone marrow biopsies, revealing malignancies. A high index of suspicion for malignancy was critical to timely diagnoses.

Keywords: Ecthyma Gangrenosum; Malignancy; Monsomy 7; Osteomyelitis; Pediatrics; Sepsis; Thrombophlebitis

Background

Cancer is among the most common causes of disease-related death in children [1,2]. The majority of pediatric cancers are hematological, and leukemia is the most common type. The incidence of Acute Lymphoblastic Leukemia (ALL) is significantly higher than other childhood leukemia, with ith Acute Myeloid Leukemia (AML) trailing at a distant second [3-5]. Myelodysplastic Syndrome (MDS) is a rare hematological malignancy that can develop into AML if untreated [6,7].

The most common presenting features of pediatric hematological malignancy include fever, malaise, bone or joint pain, hepatomegaly, splenomegaly, and lymphadenopathy [8]. Laboratory studies often show leukocytosis or cytopenias in one or more cell line. In general, these features are common to both infection and malignancy, sometimes making it difficult to distinguish between the two. This distinction can be further complicated by the fact that infection itself is a less common, but life-threatening, early manifestation of malignancy. Recognizing that an infection is the manifestation of underlying malignancy can be challenging, but is critical because delayed cancer diagnoses can lead to undesirable outcomes. Early diagnosis of cancer is more likely to result in cure and can avoid side effects caused by more aggressive treatment [9].

There is an extensive literature to educate primary care doctors about vague signs and symptoms of malignancy, including low-grade infection-like symptoms such as fever, fatigue, respiratory illness, and bone pain. However, there is surprisingly little beyond individual case reports in the pediatric infectious disease literature describing serious infection as an initial manifestation of pediatric malignancy [2,10]. This case series highlights the need for general pediatricians and infectious disease specialists to suspect underlying malignancy when presented with a severe or unusual infection that does not completely explain the clinical picture.

Cases

We report four children-two with ALL and two with MDS-who sought medical attention for unusual or severe infections that were the presenting symptom of malignancy (Table 1). In patients 1 and 2, whose cases are described in detail, the underlying malignancy was not diagnosed during their first hospitalization, delaying treatment. Patients 3 and 4 had more timely diagnoses.

Pa-	Age/ Sex	Presenting Symptoms	Infection	Organism	Clinical Clues	WBC*	Hgb*	MCV*	Plts*	ANC	Diagnosis	Time to Diagnosis
1	3F	Skin infection	Ecthyma gangrenosum	Pseudomonas aeurginosa	Pancytopenia, lack of response to antibiotics	1.6	7.2	57	58	0.99	ALL	2 Weeks
2	6F	Fever, limp, rhinorrhea	Osteomyelitis	Unknown	Neutropenia, monocytosis, macrocytosis	13.7	11.9	94	209	2.06	MDS monosomy 7	4 Months
3	18mo F	Petechiae, fever, Non-bloody non-bilious emesis, Cough	Pharyngitis, Bacteremia	Streptococcus pyogenes	Pancytopenia, Blasts on smear	4.1	9.6	82	129	0.27	ALL	At hospitalization
4	10 M	Fever, leg pain, Night sweats, Fatigue	Thrombophebitis	Fusobacterium nucleatum	Pancytopenia, Atypical infection	0.9	5.4	99	81	0.28	MDS monosomy 7	At hospitalization

*On admission. WBC= White blood count; Hgb= hemoglobin; MCV= mean corpuscular volume; Plts= platelets; ANC= absolute neutrophil count. Normal values and Units: WBC 4.5-15.5X109/L; Hgb 11.4-15.5 g/dL; Plts 140-450X109/L; ANC 1.5-8.5X109/L. Abnormal values are bold.

Table 1: Patient Summaries

Case 1

A previously healthy three-year-old girl was brought to another healthcare facility for an infected spider bite on her abdomen. She was sent home with oral cephalexin. Over the next 2 days the lesion became necrotic and increased in size, and the patient developed a fever. Physical exam was notable for right sided rales, and chest x-ray confirmed right lobar pneumonia. She was admitted and cefuroxime was started. Her blood culture was positive for gram negative rods and her antibiotics were changed to ceftazadime and gentamycin. Her abdominal lesion continued to enlarge, and she developed new lesions on her arm and ankle. Laboratory tests showed pancytopenia (Table 1). She was transferred to our institution for management of possible necrotizing fasciitis and gram-negative sepsis. On physical exam she was afebrile, with blood pressure 87/21, heart rate 126, respiratory rate 40 and oxygen saturation of 98% on 1L of oxygen. Physical examination was notable for rales in the right lung bases and a liver palpable 2cm below the right costal margin. Skin exam revealed a 6 x 7 cm purple, non-purulent necrotic lesion on her mid-thorax, a 1 x 1 cm bulla on her right ankle, and a 1.5 cm vesicle with central necrosis on her left forearm. Speciation of the positive blood cultures identified *P. aeurginosa*, and the antibiotics were changed to piperacillin/tazobactam and tobramycin. The child's condition improved. Pancytopenia in the setting of acute infection prompted a bone marrow biopsy which showed 1/39 cells were positive for monosomy 7 (a common cytogenetic abnormality in cancer, particularly MDS). This was thought to be a spurious result, and the biopsy was otherwise normal. Her labs showed resolving pancytopenia, and after two weeks, she was discharged on intravenous antibiotics. Two weeks later she returned for skin grafting and a repeat bone marrow biopsy. Labs revealed neutropenia (ANC 0.43 $x10^9$/L) and repeat bone marrow showed 60% blasts. She was diagnosed with B-cell ALL.

Case 2

A previously healthy 6-year-old girl presented to her primary care doctor with a 5-day history of low-grade fevers, rhinorrhea, right knee pain, limp, and a two-day history of fevers to 103°F. A bone scan was done that showed evidence of right lower extremity osteomyelitis. Laboratory tests (Table 1) were significant for leukocytosis, monocytosis, macrocytosis and elevated inflammatory markers (CRP 117 mg/L). The patient was diagnosed with osteomyelitis, and admitted to our hospital for intravenous clindamycin. On admission, her physical examination was notable only for fever and pain over the proximal right tibia. Over the next 5 days, the fever resolved and laboratory studies began to normalize (WBC 6x10^9/L, CRP 25 mg/L); however, at discharge she continued to have unexplained macrocytosis (MCV 94), and she developed neutropenia (ANC 0.52 x10^9/L). One week after discharge, repeat blood tests showed persistent macrocytosis and resolving neutropenia. The infections resolved, and she returned to her normal state of health. Four months after discharge a follow-up CBC showed hematologic abnormalities (MCV 91, ANC 0.05 x10^9/L). The patient was referred to the hematology/oncology service, and bone marrow biopsy showed monosomy-7-positive MDS.

Discussion

In pediatric patients with hematological malignancies, bone marrow dysfunction frequently disrupts normal host immunity, predisposing the patients to infection. Overwhelming infection, which most frequently presents as pneumonia or sepsis, can be a major life-threatening manifestation of pediatric malignancy [3]. In acute leukemia, proliferation of malignant cells within bone marrow disrupts normal hematopoiesis, often leading to neutropenia. In MDS, ineffective hematopoiesis produces abnormal leukocytes. Though children with MDS may have normal neutrophil counts, their blood cells are dysfunctional, resulting in a functional neutropenia. Abnormalities in neutrophil number and/or function increase susceptibility to infection.

Certain cytogenetic abnormalities have been linked to increased risk of infection. Monosomy 7 is the most common cytogenetic abnormality seen in childhood MDS, and it is well established that patients with monosomy 7 are prone to severe infection [11-13]. Recently, a potential molecular mechanism behind the immunodeficiency was traced to gain of function mutations in Sterile α motif domain-containing protein 9 (SAMD9) and Sterile α motif domain-containing protein 9-Like (SAMD9L) genes [14-16]. These genes are located on chromosome 7 and encode endosomal trafficking proteins. Gain of function mutations in these proteins can cause immune cell dysfunction. In patients with mutations in these genes, the gain of function mutations predate the loss of chromosome 7 and development of MDS [14,15]. Interestingly, the two patients in this case series with MDS had monosomy 7, and the initial bone marrow biopsy of patient 1, who was eventually diagnosed with ALL, was positive for monosomy 7.

When infection is the initial manifestation of malignancy it can lead to delayed cancer diagnosis. Laboratory indicators of malignancy can be misinterpreted because overwhelming infection and antibiotics can cause pancytopenia and other laboratory abnormalities. In addition, several infections, including disseminated fungal or mycobacterial infection, Epstein-Barr virus, and chronic parvovirus B19 infection, are known to clinically mimic pediatric hematological disorders [3,17,22].

The cases in this series describe children diagnosed with malignancy after a serious infection caused them to seek medical care. Several presenting features were common to multiple patients. On presentation, all patients were febrile. The patients had infectious sources for their fevers, though fever is also a common presenting symptom of pediatric malignancy [2,8]. Patients 2, 3 and 4 had pancytopenia, and all of the patients had persistent neutropenia. Macrocytosis was seen in patients 2 and 4 (94 and 99 respectively), both of whom were diagnosed with monosomy 7 positive MDS. Patient 3 was the one patient who presented with a common infection, osteomyelitis. Antibiotics resolved the osteomyelitis. However, she had persistent macrocytosis and neutropenia. It was unusual that this patient's abnormalities persisted after completion of antibiotics. The patient recovered clinically, but ongoing lab abnormalities eventually prompted a bone marrow biopsy that showed MDS. Her diagnosis was delayed 4 months after her initial presentation because, in general, her osteomyelitis followed an expected clinical course.

Patients 1, 3 and 4 had unusual infections, not normally seen in healthy children. Patient 1 was diagnosed with ecthyma gangrenosum, a cutaneous infection caused by *P. aeurginosa*. It is typically a result of pseudomonas bacteremia in a known immunocompromised, neutropenic host [19]. Patient 4 was diagnosed with *Fusobacterium nucleolatum* thrombophlebitis, a rare infection that occurs most often in patients with indwelling catheters or severe pharyngitis; it usually affects the soft tissues and venous structures of the head and neck, resulting in a clinical entity known as Lemierre's syndrome [20]. Patient 4 had *F. nucleolatum* thrombophlebitis in his lower extremity with no history of trauma, pharyngitis or intravenous catheterization. Both patients 1 and 4 had marked pancytopenia and rare infections that led to suspicion for malignancy.

Patient 3 had Group A *streptococcus* pharyngitis. Group A *streptococcus* is the most common bacterial etiology of pharyngitis in children, however, it is uncommon in children under the age of 2 and rarely invades the bloodstream when pharyngitis is the primary focus [21]. Malignancy was suspected early because the patient had petechiae on exam and 1% blasts in her peripheral smear. The presence of peripheral blasts secondary to acute infection does occur, but is unusual [22]. In this patient, workup for malignancy was started immediately.

These cases illustrate the range of infectious presentations of malignancy. In some patients there are clear clinical clues, such as the presence of peripheral blasts, which raise suspicion for malignancy. In other patients the clues to malignancy are subtle, and easily overshadowed by the infection and/or the side effects of its therapy, leading to an unfortunate delay in diagnosis.

Conclusion

At presentation, pediatric malignancy can masquerade as infection. It is critical to have a high index of suspicion for malignancy when faced with an infectious disease diagnosis that does not explain all the clinical data. An infection refractory to standard treatment, an unusual or severe infection, or resolution of an infection without resolution of laboratory data should prompt a hematology/oncology consultation and discussion of a bone marrow biopsy. Delay in malignancy diagnosis can lead to untoward consequences, including risk of additional infections and tumor progression.

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