A "SURFin' Leukemia": Acute Lymphoblastic Leukemia Masquerading as a Syndrome of Undifferentiated Recurrent Fever

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Summary: Periodic fever is not uncommon in childhood and is often ascribed to autoinflammatory conditions; however, it may be present also in children with cancer. We here describe the case of a 3-year-old boy with acute lymphoblastic leukemia who initially presented with a 4-month history of recurrent, stereotyped episodes of fever and localized joint pain, separated by completely symptom-free intervals. These symptoms were initially interpreted as a possible syndrome of undifferentiated recurrent fever until more signs of leukemia became apparent. Our report confirms that acute lymphoblastic leukemia can rarely present with periodic fever, thus possibly leading to diagnostic errors unless a high index of suspicion is maintained.

Key Words: acute lymphoblastic leukemia, children, fever, joint pain, syndrome of undifferentiated recurrent fever

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Periodic fever, that is, fever occurring with a regular pattern of distinct febrile episodes possibly associated with other symptoms, separated by symptom-free intervals, is often associated with the clinical presentation of childhood autoinflammatory conditions, including periodic fever adenitis pharyngitis syndrome, syndrome of undifferentiated recurrent fever (SURF), and monogenic autoinflammatory diseases.[1,2] Nevertheless, these symptoms should always prompt consideration for other conditions, including neoplastic disorders. Periodic fever as the presenting feature of acute lymphoblastic leukemia (ALL) has seldom been reported; therefore, it may not be considered in the differential list, possibly increasing the risk of missing the correct diagnosis unless a high index of suspicion is maintained. We here report the case of a 3-year-old child with ALL who presented with a history of periodic symptoms separated by relatively long periods of complete well-being, actually leading to some diagnostic delay.

CASE REPORT

A 3-year-old, previously healthy boy presented with a 4-month history of recurrent, stereotyped episodes of fever, refusal to bear weight, and left knee pain. There was no history of trauma nor family history of rheumatological or autoimmune diseases, tonsillectomy, or periodic fevers. Physical examination was unremarkable, with no lymphadenopathy, hepatosplenomegaly, or skin findings; the left knee examination was also unremarkable, while mild limitation of left hip external rotation was noted but only on the first of these episodes. Imaging tests were normal, including radiography and ultrasonography of the left knee and hip. Laboratory evaluation was notable for normocytic anemia (Hb 9.5 g/dL, mean corpuscular volume 77 fL), thrombocytosis (platelets 507.000/μL), a normal white blood cell (WBC) count (8.020/μL, neutrophils 3510/μL, lymphocytes 4240/μL), and markedly elevated erythrocyte sedimentation rate (ESR) (120 mm/h); all other tests, including C-reactive protein (CRP), liver function tests, and lactate dehydrogenase, were normal. Treatment with ibuprofen was prescribed each time, for 2 to 3 days, with prompt and complete resolution of symptoms. Notably, he was completely asymptomatic between episodes without taking any medications. When seen at our Rheumatology department, after 4 such episodes, he was asymptomatic and physical examination was unremarkable. The recurrence of stereotyped periodic episodes of fever and joint pain occurring almost at a regular schedule once a month raised the possibility of the relatively common periodic fever adenitis pharyngitis syndrome, but there was no pharyngeal/tonsillar involvement, so a SURF was suspected.[1,2] However, given the short time from symptom onset and the presence of localized articular pain, further diagnostic evaluation during an attack was advised before starting a therapeutic trial with single-dose oral betamethasone. Two weeks later, the child presented again with fever and knee pain. Blood tests this time showed severe anemia (Hb 7.8/dL), lymphocytosis with neutropenia (WBC 14.780/μL, N 900/μL, L 11.220/μL), a normal platelet count (212.000/μL), and elevation of inflammatory markers (CRP 38.5 mg/L, ESR 120 mm/h) and lactate dehydrogenase (471 U/L). A peripheral blood smear showed 25% lymphoid blasts, while a bone marrow smear showed 87% lymphoid

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blasts. Bone marrow immunophenotype showed 85% blasts that were positive for CD19, CD10, CD58, CD34, CD123, CD38, CD24, CD22, CD9, HLA-DR, CD13, CD33, cyCD79a, cyCD22, TdT, and negative for CD45, CD20, CD66c, CD11b, CD117, CD64, CD2, CD56, NG2, cyIgM, cyCD3, and MPO, thus confirming the diagnosis of pre-B "common" ALL. Genetic analysis identified an *ETV6/RUNX1 (TEL/AML1)* rearrangement.

DISCUSSION

This case presented several aspects that may be of interest and may have contributed to diagnostic delay. First of all, although children with ALL can present with insidious stories of protracted and often smoldering symptoms, this patient presented with periodic symptoms (ie, distinct recurrent episodes of acute symptoms, including fever and joint pain, followed by relatively long periods of complete well-being) that may have initially misled clinicians. Although fever is a common presenting symptom in children with ALL,[3] periodic fever as a presenting symptom of ALL has rarely been reported. The only report, by Koffeman et al,[4] described the case of a girl with ALL presenting with periodic fever accompanied by nonlocalized musculoskeletal pain and severe anemia. Similarly, while musculoskeletal symptoms are present in up to 18% to 32% of children with ALL, and half of them also have clinical signs of arthritis (mainly affecting the hip and the knee),[5] in our patient, joint pain occurred during febrile bouts only, thus possibly reinforcing the suspicion of a benign recurrent inflammatory condition. Therefore, a high index of suspicion should always be maintained, and laboratory and imaging tests should be performed in dubious cases when a periodic syndrome is suspected. Notably, in this case, imaging tests were all normal, blood tests were initially only partially contributive, and there were no other signs of leukemia (eg, hepatosplenomegaly or lymphadenopathy). It is already known that children with ALL presenting with joint involvement often have fewer signs of hematological disease, leading to a diagnostic delay almost double that of other patients. Brix et al[5] reported that up to 50% of such patients had 1-line cytopenia only, while 24% had no signs of cytopenia at all, and 44% had no organomegaly. In our patient, the presence of normocytic anemia on presentation should have been, a posteriori, an alarming sign, but it was probably not considered alarming enough to request a bone marrow aspirate in consideration of the fleeting symptomatology and of the fact that anemia can also be observed in some autoinflammatory conditions (eg, mevalonate kinase deficiency). This patient also had thrombocytosis, which, on the other hand, is actually more commonly observed in inflammatory conditions and was probably considered a reassuring element, even though thrombocytosis can be present in a minority of patients with ALL (3.2% in a retrospective series).[6] A markedly elevated ESR with normal CRP (so-called "acute phase reactants discordance") was seen, a finding that has been shown to represent a possible element of suspicion for neoplastic conditions but can also occur in rheumatologic or inflammatory conditions.[3,7]

In conclusion, our report confirms that periodic fever can be a presenting feature of ALL in children, particularly if it is accompanied by joint pain. Given the protean presentation of leukemia in childhood, the presence of atypical clinical and laboratory signs should always prompt a peripheral blood smear with flow cytometry and, eventually, a bone marrow aspiration. Although SURF should always be suspected in children with compatible symptoms, it remains a diagnosis of exclusion that may require time for clinical observation and further testing to exclude neoplasm, especially when a therapeutic trial of glucocorticoids is being considered.

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