Title
Burkitt-like lymphoma in a pediatric patient with familial adenomatous polyposis

Authors
Strobel, Katie M
Crane, Jacquelyn N
Bradford, Kathryn L
et al.

Publication Date
2019-11-01

DOI
10.1016/j.cancergen.2019.09.001

Peer reviewed

HHS Public Access

Author manuscript

Cancer Genet. Author manuscript; available in PMC 2021 May 15.

Published in final edited form as:

Cancer Genet. 2019 November ; 239: 33–35. doi:10.1016/j.cancergen.2019.09.001.

Burkitt-like lymphoma in a pediatric patient with familial adenomatous polyposis

Katie M. Strobel[a], **Jacquelyn N. Crane**[a,b], **Kathryn L. Bradford**[a,b], **Yalda Naeini**[c], **William A. May**[a,b,d,e], **Vivian Y. Chang**[a,b,d,e,*]

[a]Department of Pediatrics, University of California Los Angeles Mattel Children's Hospital, Los Angeles, CA, United States

[b]Division of Pediatric Hematology and Oncology, University of California Los Angeles Mattel Children's Hospital, Los Angeles, CA, United States

[c]Department of Pathology, University of California Los Angeles Hospital, Los Angeles, CA, United States

[d]Jonsson Comprehensive Cancer Center, University of California Los Angeles, United States

[e]Children's Discovery and Innovation Institute, University of California Los Angeles Hospital, Los Angeles, CA, United States

Abstract

Familial adenomatous polyposis (FAP) is an autosomal dominant condition that predisposes to multiple malignancies, most commonly colorectal carcinoma, but has rarely been associated with lymphoma. We discuss one patient found to have Burkitt-like Lymphoma (BLL) with 11q aberration in the setting of previously undiagnosed FAP. We review the literature of FAP and associated malignancies and the provisional WHO classification of Burkitt-like lymphoma with 11q aberration. Both FAP and Burkitt-like lymphoma with 11q aberration involve perturbation of the MYC network and this may provide insight into a connection between these two diagnoses. However, further study is needed to elucidate if there is an increased risk of BLL and other subtypes of lymphoma among patients with FAP in order to provide optimal counseling and surveillance for patients with FAP.

Keywords

Burkitt-like lymphoma; Familial adenomatous polyposis; 11q aberration; MYC network

Case description

Patient is a 13-year-old previously healthy male who presented with one day of right sided abdominal pain and non-bloody non-bilious emesis with exam notable for a palpable abdominal mass. An abdominal computed tomography (CT) scan demonstrated a large soft

*Corresponding author at: University of California Los Angeles Mattel Children's Hospital, Marion Davies Children's Center, 10833 Le Conte Ave, A2-410, Los Angeles, CA 90095, United States. vchang@mednet.ucla.edu (V.Y. Chang).

tissue mass in the mesentery measuring 13.3 × 10 × 9.3 cm extending from the right upper quadrant to right lower quadrant (Fig. 1A).

Family history was significant for Familial Adenomatous Polyposis (FAP) in his father, two paternal aunts, one paternal uncle and paternal grandfather. The patient's paternal grandfather underwent colectomy after his diagnosis of FAP and colonoscopy was reported notable for the presence of hundreds of polyps/adenomas. Patient's father also previously underwent colectomy. His aunts and uncles have had multiple polyps detected on screening colonoscopy. No other clinical findings of FAP had manifested in family members. The patient had not previously received genetic testing for FAP or undergone colonoscopy surveillance.

A biopsy of the abdominal mass was performed which revealed diffuse proliferation of intermediate sized atypical lymphocytes with immunoreactivity for CD20, BCL6, CD10, and c-MYC but negative for TDT, BCL2, and BCL1, with Ki67 proliferation index elevated at approximately 100% (Fig. 2A-F). Though the c-MYC immunostain was positive because it stained >40% of cells, it was weaker than the typical diffuse pattern for Burkitt Lymphoma and characteristic for cases without MYC rearrangement. Consistent with this, fluorescence in situ hybridization (FISH) showed no evidence of MYC (8q24), BCL2 (18q21), or BCL6 (3q27) rearrangement but was suggestive of trisomy 18. Additionally, FISH analysis using the MLL/KMT2A (11q23) probe detected three to six copies of the 11q-specific signal was detected in 265/300 of nuclei examined. This 11q23 region overlaps with the 11q21–23.3 region described in the new WHO entity, BLL with 11q aberration [1-5]. Overall morphologic, immunophenotypic and FISH findings were consistent with BLL with 11q aberration. Bone marrow biopsy and cerebral spinal fluid analysis were negative for lymphomatous involvement. Positron emission tomography-computed tomography (PET CT) showed that the abdominal mass previously identified on CT had intense fluorodeoxyglucose (FDG) activity with a standardized uptake value (SUV) max of 31.6 and also showed a lymph node near the stomach without other signs of disease.

Patient was started on treatment consisting of pre-phase COP,[1] two cycles of R-COPADM[2] induction, and two cycles of R-CYM[3] consolidation. After his initial pre-phase chemotherapy cycle, repeat abdominal CT scan showed significant reduction in tumor size to 7.3 × 6.2 × 7.2 cm and non-visualization of the previously seen lymph node. Repeat PET CT prior to his planned last cycle of chemotherapy was concerning for lack of complete remission with continued presence of the mass with FDG avidity with SUV max of 8.4 although it had decreased in size to 3.2 × 4.7 × 3.7 cm (Fig. 1B). Thus, he was changed to treatment received two cycles of R- CYVE.[4] Repeat PET CT at completion of therapy again showed a persistent mass in with unchanged size and FDG avidity with SUV max of 7 (Fig. 1C). Given these findings, a biopsy was performed to determine if there was histologic evidence of residual viable BLL. The biopsy showed necrotic tissue without evidence of lymphoma and no further therapy was given.

[1]Cyclophosphamide, Oncovin (vincristine), Prednisone.
[2]Rituximab-Cyclophosphamide, Oncovin (vincristine), Prednisolone, Adriamycin (doxorubicin), Methotrexate.
[3]Rituximab-CYtarabine, Methotrexate.
[4]Rituximab-CYtarabine (Ara-C), VEtoposide (VP16).

Given his family history of FAP, targeted *APC* gene sequencing was performed which showed that the patient has a heterozygous *APC* c.426_427del (p.Leu143Alafs*4) mutation consistent with a diagnosis of FAP/attenuated FAP. He was referred to our cancer predisposition clinic for further counseling and surveillance. The patient has since had his first surveillance colonoscopy which showed several adenomatous polyps without dysplasia.

Discussion

FAP is an autosomal dominant cancer predisposition syndrome caused by germline mutations in the tumor suppressor gene *APC*. If untreated, patients with FAP have nearly 100% penetrance of colorectal carcinoma [6]. Other reported malignancies in FAP include thyroid carcinoma, gastric and small intestinal adenomas and carcinomas, desmoid tumors, adrenal adenomas and carcinomas, hepatoblastoma, pancreatic cancer, and medulloblastoma.

Nonmalignant findings also described in this population include adrenal adenomas, osteomas, desmoid tumors, and dental anomalies such as hyperdontia [7]. Our patient and his family's particular *APC* mutation c 426_427 del (pLeu143Alafs*4) has been well associated with FAP. In a study examining patients with this mutation, one in 60 had an abnormal finding of an osteoma, 111 out of 120 had adenomas on colonoscopy, and 49 out of 88 had undergone colectomy [8]. Another study found multiple pilomatrixomas in siblings with a family history of colonic adenocarcinoma secondary to *APC* base pair deletions at 426-427 (AT) in exon 4 [9]. Turcot syndrome or brain tumor-polyposis syndrome are also historic eponyms that describe another variant of FAP in which patients also develop brain tumors, most commonly medulloblastoma (80% of described intracranial lesions) though ependymoma or high grade astrocytoma have also been noted [7,10]. Lymphoma appears to be exceptionally rare in FAP with only case reports described literature and no previously documented cases of Burkitt lymphoma (BL) or BLL [11-15].

Nearly all cases of BL are associated with a translocation between the site of the *c-MYC* oncogene on chromosome 8, and either the site of the Ig heavy chain gene on chromosome 14, the kappa light chain gene of chromosome 2, or the lamba light chain gene on chromosome 22 (t(8;14); t(2;8); t(8;22)) [16]. These translocations lead to the activation of the *c-MYC* oncogene. Interestingly, our patient's morphology and immunophenotype was consistent with BL but cytogenetic studies showed that our patient does not have a *c-MYC* rearrangement but, rather, has gain of 11q. Poirel and colleagues reported *MYC*-negative BL with 11q aberrancy in 2009 and later papers described additional cases [1-4, 17]. Several papers have characterized a proximal minimal gain and a telomeric minimal loss region characterizing the 11q aberration associated with the *MYC*-negative B-cell lymphoma with morphologic and immunophenotypic features of BL [2]. Although there is variability and there are multiple genes affected, in many cases the minimal gain region includes the genes *ATM, CBL, CCND1, KMT2A* (formerly called *MLL*), and *USP2* and the minimal loss region includes *FLI1, ETS1*, and *ZNF202* which have all been shown to be involved in tumorigenesis [1-4].

Additionally, pathway analysis has shown that the MYC network is affected by 11q aberration, suggesting that BLL with 11q aberrancy is a molecular variant of the *MYC* rearrangements seen in BL. In 2016, the World Health Organization (WHO) added "Burkitt-like lymphoma with 11q aberration" as a provisional entity in the classification of lymphoid neoplasms. This is described as an entity that resembles Burkitt lymphoma morphologically, immunopheno-typically, by gene expression profiling, and clinically but lacks *MYC* rearrangement [2,5].

Of note, there are also cases of *MYC*-positive BL with 11q aberration [4]. Given data that suggests that *MYC* translocation alone may not be sufficient for BL development, Grygalewicz and colleagues have proposed that both *MYC* translocation and 11q aberration may codrive the pathogenesis of cases of *MYC*-positive BL with 11q aberration [4]. Conversely, it is not clear if 11q aberration alone is sufficient for development of BLL. In one review of 11q aberration in BL, 60% had *MYC* translocation [19].

In FAP tumor development, mutations in both *APC* alleles leads to absence of functional APC protein thereby resulting in excessive accumulation of beta-catenin and transcriptional activation of Wnt signaling pathway and its target genes, including *C-MYC*, that control cell self- renewal [18,20-21]. It is reported that *C-MYC* is a target of the APC pathway [22] with studies demonstrating that the Wnt/beta-catenin pathway upregulates *C-MYC* expression in teratocarcinoma cells and lung cancer [10,23]. Thus, similar to Grygalewicz and colleagues' postulation, the perturbation of the MYC network due to FAP and the 11q aberration may have been co-drivers in the pathogenesis of BLL in this case and, therefore, FAP may modulate the risk of BLL development.

Conclusion

In summary, this is the first description of BLL in a patient with FAP, possibly mediated by 11q alterations with downstream effects in the MYC pathway. Further studies are needed to determine whether patients with FAP are at increased risk of BLL as this enable improved genetic counseling and potentially impact surveillance recommendations for patients with FAP.

Acknowledgment

The authors are grateful to Jeffrey Goldstein, MD for reviewing the pathology portion of this manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1]. Pienkowska-Grela B, Rymkiewicz G, Grygalewicz B, Woroniecka R, Krawczyk P, Czyz-Domanska K, Walewski J. Partial trisomy 11, dup(11)(q23q13), as a defect characterizing lymphomas with burkitt pathomorphology without MYC gene rearrangement. Med Oncol 2011;28:1589–95. [PubMed: 20661666]

[2]. Salaverria I, Martin-Guerrero I, Wagener R, Kreuz M, Kohler CW, Richter J, Pienkowska-Grela B, Adam P, Burkhardt B, Claviez A, Damm-Welk C, Drexler HG, Hummel M, Jaffe ES, Kuppers R,

Lefebvre C, Lisfeld J, Loffler M, Macleod RA, Nagel I, Oschlies I, Rosolowski M, Russell RB, Rymkiewicz G, Schindler D, Schlesner M, Scholtysik R, Schwaenen C, Spang R, Szczepanowski M, Trumper L, Vater I, Wessendorf S, Klapper W, Siebert RBerlin-Frankfurt-Munster Non-Hodgkin Lymphoma G. A recurrent 11q aberration pattern characterizes a subset of MYC-negative high-grade B–cell lymphomas resembling burkitt lymphoma. Blood 2014;123:1187–98. [PubMed: 24398325]

[3]. Ferreiro JF, Morscio J, Dierickx D, Marcelis L, Verhoef G, Vandenberghe P, Tousseyn T, Wlodarska I. Post-transplant molecularly defined burkitt lymphomas are frequently MYC-negative and characterized by the 11q-gain/loss pattern. Haematologica 2015;100:e275–9. [PubMed: 25795716]

[4]. Grygalewicz B, Woroniecka R, Rymkiewicz G, Rygier J, Borkowska K, Kotyl A, Blachnio K, Bystydzienski Z, Nowakowska B, Pienkowska-Grela B. The 11q–Gain/Loss aberration occurs recurrently in MYC-Negative burkitt-like lymphoma with 11q aberration, as well as MYC-Positive burkitt lymphoma and MYC-Positive high-grade B-Cell lymphoma, nos. Am J Clin Pathol 2017;149:17–28. [PubMed: 29272887]

[5]. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2016 revision of the world health organization classification of lymphoid neoplasms. Blood 2016;127:2375–90. [PubMed: 26980727]

[6]. Bisgaard ML, Fenger K, Bulow S, Niebuhr E, Mohr J. Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. Hum Mutat 1994;3:121–5. [PubMed: 8199592]

[7]. Groen EJ, Roos A, Muntinghe FL, Enting RH, de Vries J, Kleibeuker JH, Witjes MJ, Links TP, van Beek AP. Extra-intestinal manifestations of familial adenomatous polyposis. Ann Surg Oncol 2008;15:2439–50. [PubMed: 18612695]

[8]. Neklason DW, Solomon CH, Dalton AL, Kuwada SK, Burt RW. Intron 4 mutation in apc gene results in splice defect and attenuated fap phenotype. Fam Cancer 2004;3(1):35–40. doi:10.1023/B:FAME.0000026824.85766.22. [PubMed: 15131404]

[9]. Trufant J, Kurz W, Frankel A, Muthusamy V, McKinnon W, Greenblatt M, …, Bosenberg M. Familial multiple pilomatrixomas as a presentation of attenuated adenomatosis polyposis coli. J Cutan Pathol 2012;39(4):440–3. doi:10.1111/j.1600-0560.2011.01836.x. [PubMed: 22150579]

[10]. Zhang S, Li Y, Wu Y, Shi K, Bing L, Hao J. Wnt/beta-catenin signaling pathway upregulates c-MYC expression to promote cell proliferation of P19 teratocarcinoma cells. Anat Rec 2012;295:2104–13.

[11]. Frizelle FA, Hemmings CT, Whitehead MR, Spigelman AD. Familial adenomatous polyposis and duodenal lymphoma: report of a case. Dis Colon Rectum 2003;46:1698–701. [PubMed: 14668598]

[12]. Groves CJ, Saunders BP, Spigelman AD, Phillips RK. Duodenal cancer in patients with familial adenomatous polyposis (FAP): results of a 10 year prospective study. Gut 2002;50:636–41. [PubMed: 11950808]

[13]. Jagelman DG, DeCosse JJ, Bussey HJ. Upper gastrointestinal cancer in familial adenomatous polyposis. Lancet 1988;1:1149–51 [PubMed: 2896968]

[14]. Kamarashev J, Dummer R, Schmidt MH, Kempf W, Kurrer MO, Burg G. Primary cutaneous T-cell-rich B-cell lymphoma and hodgkin's disease in a patient with gardner's syndrome. Dermatology 2000;201:362–5. [PubMed: 11146353]

[15]. Nugent KP, Spigelman AD, Phillips RK. Life expectancy after colectomy and ileorectal anastomosis for familial adenomatous polyposis. Dis Colon Rectum 1993;36:1059–62. [PubMed: 8223060]

[16]. Berger R, Bernheim A. Cytogenetics of burkitt's lymphoma-leukaemia: a review. IARC Sci Publ 1985:65–80.

[17]. Poirel HA, Cairo MS, Heerema NA, Swansbury J, Auperin A, Launay E, Sanger WG, Talley P, Perkins SL, Raphael M, McCarthy K, Sposto R, Gerrard M, Bernheim A, Patte C, Committee FLIS. Specific cytogenetic abnormalities are associated with a significantly inferior outcome in children and adolescents with mature B-cell non-Hodgkin's lymphoma: results of the fab/lmb 96 international study. Leukemia 2009;23:323–31. [PubMed: 19020548]

[18]. Clevers H. Wnt/beta-catenin signaling in development and disease. Cell 2006;127:469–80. [PubMed: 17081971]

[19]. Gonzalez-Farre B, Ramis-Zaldivar JE, Salmeron-Villalobos J, Balague O, Celis V, Verdu-Amoros J, …, Salaverria I. Burkitt-like lymphoma with 11q aberration: A germinal center derived lymphoma genetically unrelated to burkitt lymphoma. Haematologica 2019. doi:10.3324/haematol.2018.207928.

[20]. Rubinfeld B, Souza B, Albert 1, Muller O, Chamberlain SH, Masiarz FR, Munemitsu S, Polakis P. Association of the apc gene product with beta-catenin. Science 1993;262:1731–4. [PubMed: 8259518]

[21]. Rustgi AK. The genetics of hereditary colon cancer. Genes Dev 2007;21:2525–38. [PubMed: 17938238]

[22]. He TC, Sparks AB, Rago C, Hermeking H, Zawel L, da Costa LT, Morin PJ, Vogelstein B, Kinzler KW. Identification of c-MYC as a target of the apc pathway. Science 1998;281:1509–12. [PubMed: 9727977]

[23]. Juan J, Muraguchi T, 1ezza G, Sears RC, McMahon M. Diminished wnt ->beta-catenin ->c-MYC signaling is a barrier for malignant progression of BRAFV600E-induced lung tumors. Genes Dev 2014;28:561–75. [PubMed: 24589553]

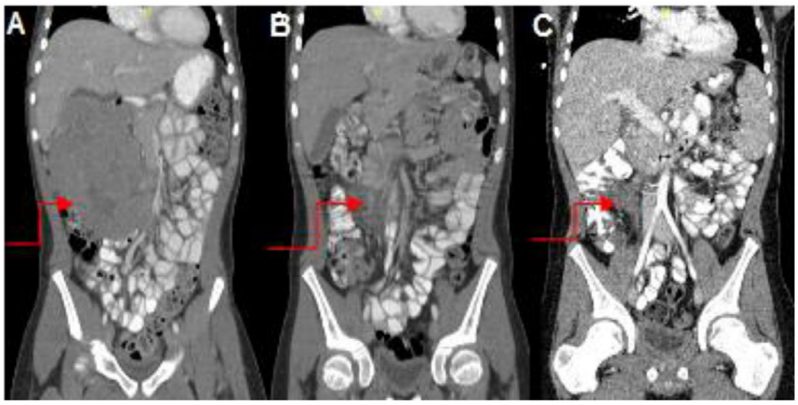

Fig. 1.

Imaging. (A) Initial CT with abdominal mass measuring 11 × 16.9 × 10.5 cm. (B) CT after pre-phase and four cycles of chemotherapy showing decreased size of the mass. (C) End of therapy CT with unchanged size of the mass compared to prior. Red arrows indicate site of mass.

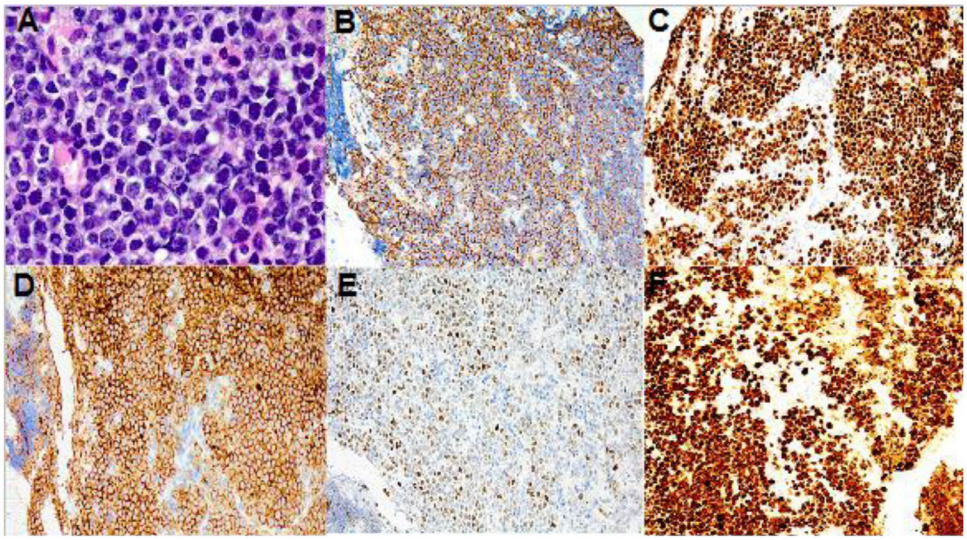

Fig. 2.

Diagnostic biopsy pathology. (A) Microscopic exam shows diffuse proliferation of intermediate sized atypical lymphocytes with scattered tingible body macrophages in a “starry sky” pattern. Immunohistochemical studies show cells that are positive for (B) CD20; (C) BCL6; (D) CD10; (E) CMYC; (F) with Ki67 proliferation is estimated at 100%.