In implant associated lymphomas, prosthesis explantation and complete excision of any residual mass are the recommended approaches. Systemic chemotherapy is generally recommended for patients with locally advanced and disseminated diseases, mainly using treatment protocols routinely adopted for systemic ALCLs (e.g., CHOP, CHOEP, etc.). Limited data are available regarding the treatment of non-mammary implant associated ALCL. The first documented joint prosthesis associated ALCL patient was lost to follow-up while no adjuvant chemotherapy was considered in gluteal implant associated ALCL, however the patient was disease free. Our patient has received chemotherapy (CHOP regime) and was doing well at last follow-up.

In conclusion, oncologists and pathologists should be more observant in patients who undergo silicone or non-silicone device implantation as these surgical procedures will continue to rise in various non-neoplastic and neoplastic lesions. Though the morphology and immunophenotyping of mammary and non-mammary implant associated ALCL is similar to ALK-negative ALCL, such cases need to be further investigated for *DUSP22* or *TP63* rearrangements as the latter carries dismal prognosis. The exact biological relationship between the implant device and ALCL needs to be addressed and explored at the molecular level.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

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DOI: <https://doi.org/10.1016/j.pathol.2020.06.022>

Metachronous and clonally related classic Hodgkin lymphoma and nodular lymphocyte predominant Hodgkin lymphoma

Sir,

Classic Hodgkin lymphoma (CHL) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) are two distinct subtypes of Hodgkin lymphoma by the World Health Organization (WHO) classification.¹ They share some common clinical and pathological features, but are different in immunophenotype, inflammatory background, and genetic characteristics. The coexistence of CHL and NLPHL in the same patient is exceedingly rare.² We present a case of CHL where complete remission was achieved after treatment, but clonally related NLPHL developed subsequently.

A previously healthy 14-year-old male presented with generalised lymphadenopathy. He had no B symptoms. His uncle had a history of CHL. The computed tomography (CT) scan revealed lymphadenopathy in the left neck, bilateral supraclavicular, left axilla, anterior mediastinum and right hilum, and multiple low attenuating lesions in the spleen. The positron emission tomography (PET) scan confirmed glucose avid lymphadenopathy of these areas with a maximum SUV of 16.1 at right hilum. An excisional biopsy of left supraclavicular lymph node showed a nodular infiltrate dissected by thick fibrotic bands (Fig. 1A). The infiltrate was composed of scattered large Hodgkin/Reed–Sternberg (HRS) cells in a background of small lymphocytes, eosinophils, histiocytes, and plasma cells (Fig. 1B). The HRS cells were positive for PAX5 (weak), CD15 and CD30, and negative for CD20, CD45 and EMA (Fig. 1C–F). *In situ* hybridisation for EBV encoded small RNA (EBER) was negative. The findings were consistent with nodular sclerosis CHL. The cytogenetic analysis revealed a complex karyotype with an abnormal hypertriploid clone characterised by additional unknown material on Xq, 1q, 2p, and 7q, isochromosomes of 7p and 10q, gain of 1, 2, 10, 19, and 5–6 marker chromosomes and loss of 6 and 17 {78–79,XY,add(X)(q?24),+1,add(1)(q32)x2,+2,add(2)(p16)x2,-6,+add(7)(q31)x2,i(7)(p10),+10,i(10)(q10)x2,-17,+19,+5–6mar[5]/46,XY[10]}. The patient's bone marrow was not involved by the CHL. He was designated stage IIIS CHL and was treated per Children's Oncology Group (COG) protocol AHOD0031 for intermediate risk Hodgkin disease. He received four cycles of ABVE-PC (adriamycin, bleomycin, vincristine sulfate, etoposide, prednisone and cyclophosphamide). Post-chemotherapy the CT scan showed resolution of lymphadenopathy and splenic mass. The PET scan showed no convincing evidence of residual lymphoma. He subsequently received radiation therapy of 2100 cGy to the neck, mediastinum and spleen. He was in clinical remission.

Fig. 1 H&E (A) low power and (B) high power of classic Hodgkin lymphoma. Hodgkin/Reed–Sternberg (HRS) cells are positive for (C) CD30 and (D) CD15, and are negative for (E) CD20 and (F) CD45. H&E (G) low power and (H) high power of nodular lymphocyte predominant Hodgkin lymphoma. Lymphocyte predominant (LP) cells are positive for (I) CD20 and (J) partial CD30, but negative for (K) CD15. (L) PD1 demonstrates PD1+ T-cells forming rosettes around LP cells.

Fifty-two months later, he developed left cervical lymphadenopathy (2.7×1.9 cm), which was incidentally found by a CT scan. A subsequent PET scan revealed markedly hypermetabolic left cervical lymphadenopathy with a maximum SUV of 17.5. Examination of the abdomen and pelvis showed normal uptake. He denied any B symptoms. The biopsy of this lymph node revealed a vaguely nodular infiltrate effacing the normal architecture of lymph node (Fig. 1G). The nodules contained small lymphocytes admixed with scattered, large lymphocyte predominant (LP) cells (Fig. 1H). Eosinophils were absent. The LP cells were

positive for CD20, CD79a, PAX5, partial CD30, CD45, BCL6, EMA, and IgD, but negative for CD15 and MUM1 (Fig. 1I–K). CD21 highlighted expanded follicular dendritic meshworks. Characteristic LP cells rosetting by small T cells were highlighted by CD3 and PD1 immunostains (Fig. 1L). The background cells in the nodules were predominantly small B-cells. EBER *in situ* hybridisation was negative. These features were consistent with NLPHL. There was no cytogenetic evidence of an abnormal clone. The patient's bone marrow was again negative for lymphoma involvement. He was treated with two cycles of ICE (ifosfamide,

carboplatin and etoposide) chemotherapy. A follow-up PET scan showed resolution of hypermetabolic activity in cervical node. He underwent autologous peripheral blood stem cell transplant after consolidation with BEAM (carmustine, etoposide, cytarabine, and melphalan). He received rituximab on day +30 post-transplant and completed 16 days of involved field radiotherapy (total 30.6 Gy) on day +60 post-transplant. Currently he has remained disease free for 93 months post-transplantation.

Next generation sequencing (NGS) was used to analyse the *IGK* gene rearrangement on the DNA extracted from tissue of CHL and NLPHL. DNA was amplified according to the manufacturer instructions using the LymphoTrack *IGK* Assay Panels (Invivoscribe Technologies, USA). PCR amplicons were quantified using the KAPA library quantification kit (Hoffman-La Roche, Switzerland). The barcoded *IGK* libraries were pooled and sequenced on the MiSeq Dx using the MiSeq Reagent Kit v3 (Illumina, USA). The sequencing data were analysed using the LymphoTrack Software MiSeq v2.11 package (Invivoscribe Technologies). The merged reads (1 or 2 nucleotides difference) were used to determine clonality for the *IGK* assay. If the percentage of total reads for a merged *IGK* sequence was higher than 2% and four-fold greater than the tenth most common merged sequence, it was designated as a clonal population. The same clonal *IGK* rearrangement (V3D-20 J1) was identified from both samples with identical sequences (Fig. 2), which supported that these two tumours were clonally related.

CHL and NLPHL account for 90% and 10% of Hodgkin lymphoma, respectively.¹ It is extremely rare that CHL and NLPHL occur in the same patient. In the study from Stanford, five patients were found to have both CHL and NLPHL simultaneously or consecutively among 4748 diagnoses of Hodgkin disease (including CHL and NLPHL) between 1980 and 1992.² We performed an English literature search for the reported cases in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) using different combinations of key words in the title/abstract field, including 'composite/coexist/metachronous lymphoma, Hodgkin disease/lymphoma, nodular lymphocyte predominant Hodgkin lymphoma.' A total of nine cases have been reported in the literature, including six metachronous cases, two patients with composite lymphoma, and one synchronous case but at different sites (Table 1).^{2–5} All the cases were young to

middle aged male patients, ranging from 10–48 years with a median age of 22 years. Among seven patients with the initial staging information, three presented with localised lymphadenopathy (stage I) and four with advanced stage disease (stage III). The bone marrow was spared in all patients. Three patients developed NLPHL preceding CHL, whereas four had CHL before NLPHL. Among seven metachronous cases, the average time interval to develop the second lymphoma was 9.5 years. Mixed cellularity CHL and nodular sclerosis CHL each comprised 50% of the cases. A clonal *IGK* or *IGH* gene rearrangement was found on the cases with coexistence of CHL and NLPHL (Cases 8 and 9), but clonal relationship was not investigated on other reported metachronous cases. Herein, we showed a clonal relationship between CHL and NLPHL in a metachronous case. The presence of both entities in a same patient and a clonal relationship suggest HRS and LP cells can derive from a common B-cell precursor.

CHL in a first degree relative is associated with an increased risk of developing CHL and other lymphoproliferative diseases, and a male predominance was found in familial HL cases.^{6–8} The father and paternal first and third cousins of Case 8 all had CHL; his paternal grandfather and the first cousin had acute leukaemia.³ Our patient's uncle had a history of CHL. Both cases suggest a genetic component in HL development.

NGS was used to analyse the *IGK* gene rearrangements in our study. The advantages of using NGS over traditional polymerase chain reaction (PCR) based *IGH/IGK* clonality assay include enhanced sensitivity, specificity, and objectivity, and allowing investigators to monitor and track clonal evolution through the entire course of the disease. Microdissection of HRS or LP cells is not required for NGS based *IGK* assay. The percentages of total reads of identical *IGK* sequence detected in CHL and NLPHL were 3.7% and 3.9%, comparable to the low percentages of Hodgkin cells in the specimens.

Our patient illustrates a rare case of metachronous, clonally related CHL and NLPHL. It is challenging for pathologists to diagnose, as well as for clinicians to treat such patients, especially cases with concurrent composite Hodgkin lymphoma. Limited tissue such as needle core biopsy can be problematic and a large excision is generally required for a diagnosis of such cases. Given the unpredictable nature of

Range 1: 1 to 149 [Graphics](#) ▼ Next Match ▲ Previous Match

Score	Expect	Identities	Gaps	Strand
276 bits(149)	1e-79	149/149(100%)	0/149(0%)	Plus/Plus
CHL	AGCAGGGCCACTGGCATCCCAGACAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACT	60		
NLPHL	AGCAGGGCCACTGGCATCCCAGACAGGTTTCAGTGGCAGTGGGTCTGGGACAGACTTCACT	60		
CHL	CTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGT	120		
NLPHL	CTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGTGTATTACTGTCAGCAGTATGGT	120		
CHL	AGCTCACCGTGGACGTTTCGGCCAAGGGAC	149		
NLPHL	AGCTCACCGTGGACGTTTCGGCCAAGGGAC	149		

Fig. 2 Identical *IGK* clone found in both classic Hodgkin lymphoma (CHL) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). The sequences (V3D-20 J1) from CHL and NLPHL are the same.

Table 1 A review of coexisting CHL and NLPHL cases

Case	Type	Age/ Sex	First Bx site/Dx	BM	Initial stage	Therapy	Response	Second Bx site/Dx	Time interval (years)	Clonal relationship	LMP/ EBER	Status/ follow up (years)	Reference
1	Metachronous	21/M	LN: NLPHL	N/A	N/A	N/A	N/A	Spleen: CHL, MC	5	ND	N/A	Alive/6	4
2	Metachronous	17/M	LN: NLPHL	Neg	IA	Roentgen therapy	N/A	LN (same site): CHL,MC	17	ND	N/A	Dead/19	4
3	Metachronous	10/M	LN: CHL, MC	Neg	IA/IB	XRT+Chemo	CR	LN (diff. site) NLPHL	18	ND	LMP/—	N/A	2
4	Metachronous	30/M	LN: CHL, NS	Neg	IIIAS	Auto BMT	N/A	LN (same site): NLPHL	10	ND	LMP/—	Dead/11	2
5	Metachronous	22/M	LN: CHL, NS	Neg	IIIAS	ABVD	PR	LN (diff. site): NLPHL	5	ND	LMP/—	N/A	2
6	Metachronous	27/M	LN: NLPHL	N/A	N/A	Adriamycin, vinblastine sulfate, VP16	PR	LN (same site): CHL,NS	3	ND	LMP/—	N/A	2
7	Composite	22/M	LN: CHL,MC + NLPHL	Neg	IA/IB	XRT	CR	NA	NA	ND	ND	N/A	2
8	Synchronous	24/M	Thymic mass: CHL,NS Parotid mass: NLPHL	Neg	N/A	N/A	N/A	NA	NA	Clonally related	EBER/ both —	N/A	3
9	Composite	48/M	LN:CHL,MC + NLPHL	Neg	IIIA	ABVD+ XRT+ BEACOPP	CR	NA	NA	Clonally related	EBER CHL/+ NLPHL/ —	Alive/1.8	5
10	Metachronous	14/M	LN: CHL, NS	Neg	IIIAS	ABVE-PC+ XRT	CR	LN (diff. site) NLPHL	4.3	Clonally related	EBER/ both —	Alive/7.8	Current case

ABVD, adriamycin, bleomycin, vinblastine sulfate, dacarbazine; ABVE-PC, adriamycin, bleomycin, vincristine sulfate, etoposide, prednisone and cyclophosphamide; BEACOPP, cyclophosphamide, doxorubicin, etoposide phosphate, naltrexone, vincristine, bleomycin; BMT, bone marrow transplant; Bx, biopsy; Chemo, chemotherapy; CHL, classic Hodgkin lymphoma; CR, complete remission; diff, different; Dx, diagnosis; EBER, EBV-encoded RNA; F, female; LMP, latent membrane protein; LN, lymph node; M, male; MC, mixed-cellularity; NA, not applicable; N/A, not available; ND, not done; Neg, negative; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; NS, nodular sclerosis; PR, partial remission; XRT, radiotherapy.

recurrent disease, biopsy of the relapsed lesion is essential for diagnosis and treatment purposes.

Conflicts of interest and sources of funding: The authors state that there are no conflicts of interest to disclose.

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DOI: <https://doi.org/10.1016/j.pathol.2020.06.019>

The lipid profile in children prior to isotretinoin therapy: an opportunity to detect familial hypercholesterolaemia

Sir,

Familial hypercholesterolaemia (FH) is an autosomal dominant disorder of low density lipoprotein (LDL) catabolism associated with elevated LDL cholesterol and premature atherosclerotic coronary artery disease (CAD).¹ FH has been shown to be more prevalent than previously thought, occurring in ~1:250 people.^{2,3} However, the vast majority of individuals with FH are undiagnosed and often under treated.¹ A recent study demonstrated that initiation of statin therapy in childhood was associated with reduced coronary artery disease.⁴ FH is predominantly caused by variants in the LDL receptor (*LDLR*), apolipoprotein B (*APOB*) or proprotein