

Excellent Outcomes of Grey Zone Lymphoma: Case Series of Paediatric Patients Treated at a Single Centre

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Abstract

Our objective was to review clinical presentation, treatment protocol used and its efficacy and effectiveness in patients of grey zone lymphoma during last 5 years at our centre.

A retrospective chart review of children below 18 years of age was done from 2011 to 2016. A proforma was devised for this purpose and the findings of cases detected during the specified period were noted over it. We treated 4 cases, all with a diagnosis of Grey Zone Lymphoma of ages 13, 13, 15 and 7 years at presentation and all were males. Two patients had stage II and the other two had stage III disease. None had a mediastinal mass. All patients were treated according to UKCCSG NHL guidelines. Tumour lysis syndrome was not observed in any child. All tolerated chemotherapy very well and achieved complete remission. No patient died of the disease or any complication and all are well on their latest follow ups.

To conclude from excellent outcomes in our case series, we recommend that children with Grey Zone Lymphoma should be treated according to Non-Hodgkin Lymphoma treatment guidelines. However we need to have more prospective studies, so that treatment guidelines can be established.

Keyword: Grey Zone Lymphoma (GZL), treatment, outcome

Introduction

A lymphoma which demonstrates transitional morphologic and immunophenotypic features between classical Hodgkin's lymphoma (CHL) and large B- cell lymphoma (diffuse large B cell lymphoma and Burkitt's lymphoma), mostly presenting with a mediastinal but occasionally with a peripheral lymph node disease is termed as grey zone lymphoma (GZL) as shown in figure 2.^{1,2} The terms "gray zone or grey zone or unclassifiable

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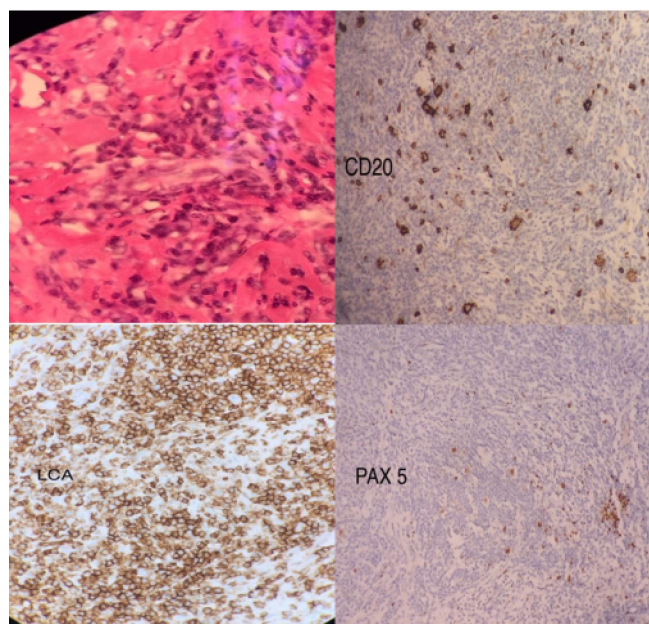


Figure-1: Histopathology Images of Grey Zone Lymphoma.

or indeterminate or mediastinal grey zone lymphoma (MGZL)" are synonymous and are used interchangeably.^{3,4} The outcome of these cases may differ from DLBCL & CHL.⁵

These lymphomas may show three types of features:

- 1) A morphology resembling CHL in one area and DLBCL/Burkitt's lymphoma (BL) in another.
- 2) A morphology which may show an overlap between the CHL and DLBCL/BL.
- 3) The morphology may be compatible with the diagnosis CHL but the immunophenotyping favours DLBCL/BL.^{5,7}

The tumour cells are often pleomorphic and grow in a diffusely fibrotic stroma. Immunophenotyping of these tumours may show positive CD 45, CD 20, CD 79a and CD30 whereas CD 15 may or may not be positive. PAX5, OCT-2, and BOB1 may also be positive as shown in figure 1 and described in table 3.⁸

No data based on cytogenetics is available for these tumours although genetic aberrations involving 2p and 9p have been detected in CHL and DLBCL.^{1,9,13}

Table-1: Clinical characteristics.

Case	Age	Sex	Fever	Wt. loss	Night Sweats	Seizures	Pallor	Lymphadenopathy	Visceromegaly	Chest mass	TLS	LDH U/L
1	13 Y	M	No	No	No	No	No	Yes	Yes	No	No	429
2	13 Y	M	No	No	No	No	Yes	Yes	No	No	No	795
3	13 Y	M	No	No	No	No	No	Yes	No	No	No	361
4	7 Y	M	No	No	No	No	No	Yes	No	No	No	372

Table-2: Stage, treatment protocol and outcome.

Case	Stage	NHL group	Remission	Date	Status	Follow-up	Survival
1	II	NHL group B	Remission	09-09-14	Alive	16-08-17	35 months
2	III	NHL group B	Remission	23-07-14	Alive	21-07-17	36 months
3	III	NHL group B	Remission	21-04-14	Alive	05-05-17	36 months
4	II	NHL group B	Remission	09-11-16	Alive	05-06-17	7 months

Table-3: Morphology and immunohistochemical stains.

Case	Morphology	CD 15	CD 20	CD 30	CD 45	PAX 5	CD 79a	CD 3	ALK	LCA
1	Predominantly Hodgkin lymphoma	-	+	+	NA	-	-	NA	-	-
2	Mixed features	+	+	+	NA	+	Weak +	-	NA	+
3	Mixed features	-	+	+	NA	NA	NA	-	-	-
4	Predominantly Hodgkin lymphoma	-	+	+	+	+	NA	-	NA	NA

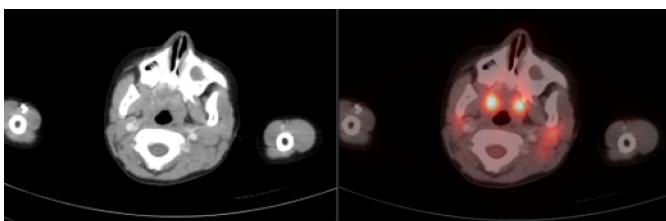


Figure-2: PET CT Image of Grey Zone Lymphoma.

The clinical features of these tumours are similar to their parent tumours (CHL & DLBCL) except that these appear to be more common in males than females as illustrated in table 1.^{14,15}

These rare tumours have been included in the WHO classification and only a few studies have reported their outcomes.¹⁶ In one study the survival of these patients was found to be significantly inferior to other HLs.¹⁷ The regimens like DA-EPOCH-R have been found to be reasonable for these patients. Although a proportion of these patients can be cured with immunochemotherapy alone but they are more likely to require radiation therapy than patients with DLBCL. The future strategies include targeted therapies like the use of Janus Kinase Inhibitors.¹⁸ We are reporting a series of four cases that presented at our centre and were diagnosed as grey cell lymphoma.

Case Series

A retrospective chart review was done from 2011 to 2016 to find out the clinical and radiological features, treatment and outcome of children who presented with grey zone

lymphoma below 18 years of age. A proforma was devised for this purpose and findings of four cases detected during the specified period were noted over it. Our institutional review board approved this study.

We found 4 cases with a diagnosis of grey zone lymphoma of ages 13, 13, 15 and 7 years at presentation and all were males. Two of these patients belonged to Khyber Pakhtunkhwa (FATA and Peshawar), one came for Sindh (Karachi) and one was resident of Baluchistan (Quetta) province of Pakistan. All patients were staged according to Cotswolds revision of the classical Ann Arbor staging system.¹⁹ Two patients had stage II and the other two had stage III disease. All patients were treated according to UKCCSG NHL guidelines- Group B with initial cyto-reduction with COP (cyclophosphamide, vincristine and prednisolone), followed by two cycles of COPADM (cyclophosphamide, vincristine, prednisolone, doxorubicin and methotrexate) and two cycles of CYM (cytarabine and methotrexate).²⁰ Tumour lysis syndrome was not observed in any child; all tolerated chemotherapy very well and achieved complete remission. None of these patients received radiotherapy. No patient died of the disease or any treatment complications. All patients are in morphological remission and clinically well on their latest follow up visit. Table 2 gives a comprehensive description of stage, treatment protocol and outcome of each patient treated at our centre.

Discussion

Above is a brief description of four children who had GZL and were treated at a single centre in a developing country. As described earlier, GZL shares clinical characteristics of both Classical Hodgkin Lymphoma and Large B Cell Lymphoma (Burkitt's lymphoma and diffuse large B cell lymphoma). Patients are mostly adolescents, present with nodular swellings or bulky mediastinal masses, mostly they are males and LDH is usually within normal range.^{1,21} Case 1 and case 4 had a pre-dominant Hodgkin lymphoma morphology, while case 2 and 3 had mixed morphological features. CD 20 and CD 30 were found to be positive in all patients and only case 2 had malignant cells which expressed CD 15. All except one patient presented as adolescents except case 4 who was 7 years old at presentation. Interestingly, none of the patients had mediastinal mass, which is unusual for these patients according to literature. All cases were males and only case 2 had high LDH on baseline.

All the patients were treated according to UKCCSG NHL guidelines and treatment was decided after discussion of each case individually in paediatric lymphoma conferences.²⁰ In the past, both HL-based and NHL-based regimens have been tried with similar outcomes in both.²¹ The rationale behind giving NHL-based chemotherapy to our patients was that we wanted to treat these children with a more intensive regimen as there was an air of uncertainty about chemotherapeutic agents used in the past due to the higher drug resistance. Due to rarity of this condition, no clinical trials have been carried out and we are yet to design guidelines to treat such cases.

According to some recent studies, the GZLs have poorer outcome as compared to other aggressive B-cell lymphomas.²² However, all our patients are doing well after end of treatment until their last follow ups as mentioned above.

Conclusion

In our case series of 4 patients we report excellent outcomes. Therefore, we recommend that these children should be treated according to Non-Hodgkin Lymphoma treatment guidelines. However, since this is an uncommon diagnosis, we need to have more prospective studies so that treatment guidelines can be established.

Disclaimer: The abstract of this case series has not been presented or published in any conference and manuscript

was not part of any research, PhD or any other relevant information.

Conflict of Interest: The authors declare that there is no conflict of interest.

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