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Conflict of interest

All authors declare no competing interests.

Author contributions

Christina Y.C. Yip, Shir Ying Lee, Eng Soo Yap designed the study, acquired and analysed the data and wrote the paper. Winnie Z.Y. Teo, Chun-Tsu Lee and Sanjay De Mel, designed the study, acquired the data and contributed to the manuscript. Sheryl Kan, Melvin C.C. Lee and Will N.H. Loh acquired the data and critically reviewed the manuscript. Er Luen Lim analysed the data and critically reviewed the manuscript.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. ROC analysis for lymphocyte parameters in differentiating mild from severe and critical COVID-19.

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Atypical lymphocytes in peripheral blood of patients with COVID-19

The outbreak of coronavirus disease 2019 (COVID-19) in December 2019 in Wuhan, China, rapidly became a pandemic across the world, including the USA. Since March 2020, we started to receive peripheral blood smear review consults for patients who were admitted with COVID-19. We reviewed 15 peripheral blood smears from the 15 most

Table I. Full blood count of the 15 patients with COVID-19 accompanying the blood smear review in Fig 1.

ID no.	Age, years	Location/ disposition	% atypical Lympho.	WBC, K/μl	RBC, M/μl	Hb, g/l	Hct, %	MCV, fl	MCH, pg	MCHC, %	RDW, %	PLT, K/μl	MPV, fl	Absolute neutrophil, K/μl	Absolute lymphocyte, K/μl	Absolute monocyte, K/μl	Absolute eosinophil, K/μl	Absolute basophil, K/μl
1	72	ICU	10	16	2·03	68	21·6	106	33·5	31·5	14·6	287	11·2	11·4	3	0·2	0·2	0·2
2	43	Medicine Floor	0·5	3·9	2·93	83	27·5	94	28·3	30·2	12·1	228	10·6	1·8	1·5	0·5	0	0
3	37	ED	14	7·5	4·45	118	35·4	80	26·5	33·3	15·6	73	12·6	6·2	0·7	0·4	0	0·1
4	66	ICU	9	14·6	2·36	71	24·5	104	30·1	29	16·9	407	11·2	11·1	0·6	2	0	0·1
5	68	ICU	2	10·6	2·41	71	22·3	92	29·5	31·8	13·7	232	11	8·8	1	0·7	0·1	0
6	54	ICU	13·5	13·5	2·58	73	23·1	90	28·3	31·6	16·4	229	11·1	11·2	0·5	1·1	0·1	0·1
7	58	Medicine Floor	12	8·4	5·7	166	49·1	86	29·1	33·8	12·9	315	10·7	6·4	1·5	0·5	0	0
8	75	ICU	6	9·6	3·73	108	29·8	80	29	36·2	15	144	10·9	8	1·1	0·3	0·1	0
9	42	ICU	4	23·7	2·56	78	24·5	96	30·5	31·8	15·8	158	12·9	20·4	1·2	2·1	0	0
10	65	ICU	9	18·8	2·96	74	24·5	83	25	30·2	18·2	443	11·7	15·6	1·5	1·7	0	0
11	70	Medicine Floor	6	2·3	5·56	125	41·9	75	22·5	29·8	16·7	76	N/A	1·6	0·5	0·2	0·1	0
12	26	Medicine Floor	3	1·6	3·46	107	31·9	92	30·9	33·5	12·8	207	10·3	0·8	0·4	0·4	0	0
13	90	ICU	4	17·1	4·2	113	35·7	85	26·9	31·7	16·7	65	N/A	15·7	0·5	0·3	0	0
14	54	Medicine Floor	10	1·9	2·65	84	24·4	92	31·7	34·4	11·9	122	10·7	1·3	0·2	0·2	0	0
15	72	ICU	0	4	3·94	117	34·7	88	29·7	33·7	12·2	97	9·5	2·2	1·5	0·2	0	0

Hb, haemoglobin; Hct, haematocrit; ICU, intensive care unit; ID, identification; MCH(C), mean corpuscular Hb (concentration); MCV, mean corpuscular volume; MPV, mean platelet volume; RBC, red blood cell; PLT, platelets; RDW, red cell distribution width; WBC, white blood cell.

recently admitted patients Table I. These patients ranged in age from 26 to 90 years and included eight males and seven females. The reasons for peripheral blood smear consult were primarily concerns for haemolysis (nine of the 15 cases), followed by anaemia, thrombocytopenia and pancytopenia.

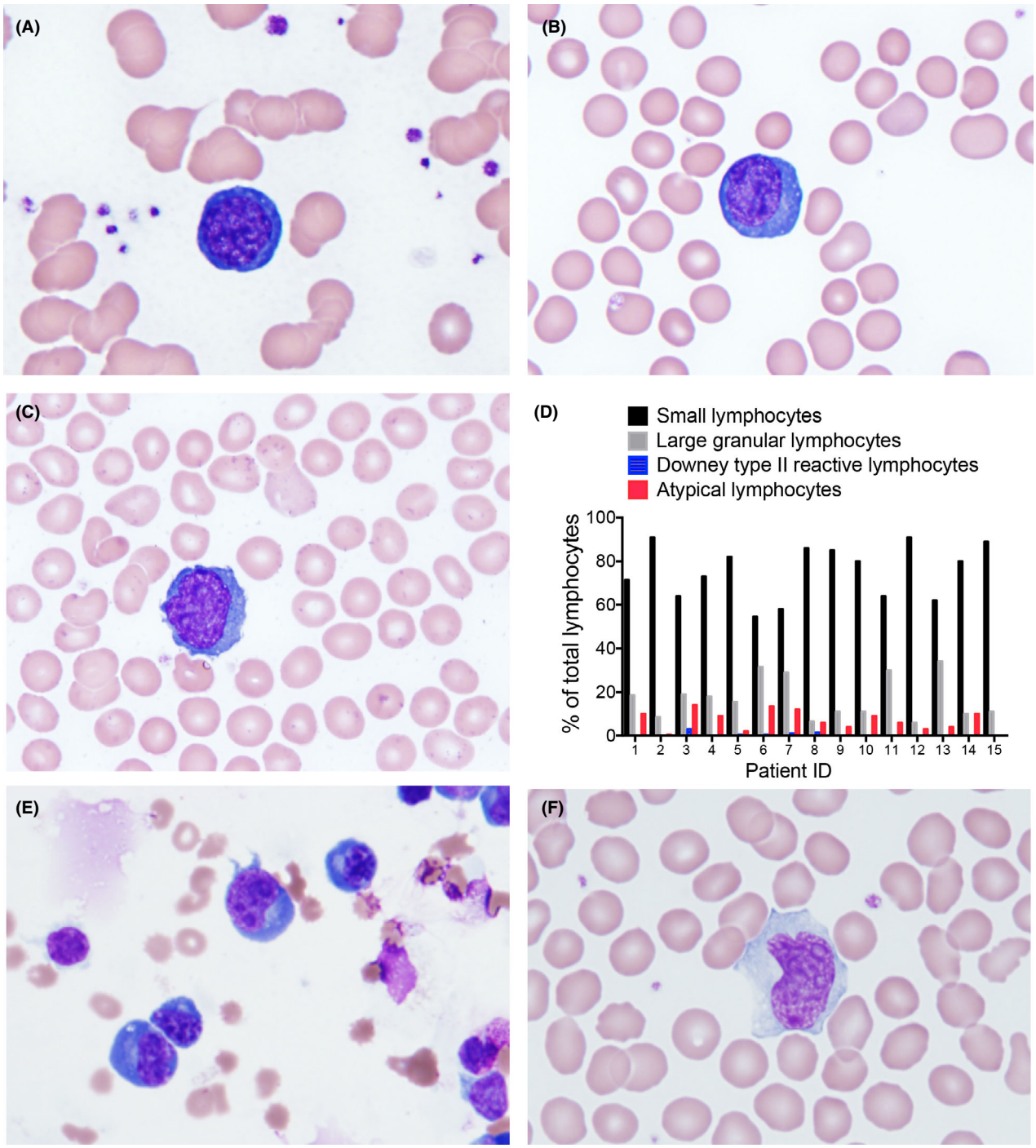

Fig 1. Atypical lymphocytes in patients with COVID-19. (A–C) Wright-Giemsa stained peripheral blood smear showing representative forms of atypical lymphocytes observed in 15 cases of smear review (×100). (D) Percentages of indicated lymphocytes out of total lymphocytes in the patients with COVID-19. Differential count of the indicated lymphocytes was performed; 200 lymphocytes were counted in each patient. (E) Wright-Giemsa stained bronchial alveolar lavage smear from a patient with COVID-19 (×60). (F) Wright-Giemsa stain of the peripheral blood smear from a patient with infectious mononucleosis caused by Epstein–Barr virus infection (×100).

Most of the patients showed normocytic anaemia with mild anisopoikilocytosis. None of the reviewed cases showed morphological evidence of haemolysis, regardless of their clinical presentation. Seven patients had neutrophilia and two had neutropenia, while the neutrophil counts were normal in six patients. The lymphocyte count was at a lower normal range in eight patients (normal range 1·0–4·0 K/μl) and seven patients had lymphopenia. Besides these findings, the most common observation was the presence of atypical lymphocytes in most of the smears (14/15, 93·3%). These lymphocytes are medium to large in size with loosely condensed chromatin, and moderate to deep basophilic cytoplasm Fig 1A. Some of these cells demonstrate plasmacytoid morphology with eccentric nuclei and perinuclear hof Fig 1B. Some show visible nucleoli resembling immunoblasts Fig 1C. The atypical lymphocytes comprised 6·94 ± 4·30% of the total lymphocytes Fig 1D. It appears that the percentage of atypical lymphocytes in total lymphocytes does not correlate with the severity of the disease Table I. Additionally, two cases of bronchial alveolar lavage smears from two patients (no accompanying blood smear review) were reviewed due to the presence of numerous atypical lymphocytes with the same morphology as those found in the blood smear Fig 1E.

These atypical lymphocytes are likely reactive to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Their morphology is different from Downey type II reactive lymphocytes Fig 1F that are commonly seen in other viral infections such as Epstein–Barr virus. In our reviewed 15 patients, Downey type II reactive lymphocytes were seen, but with a much lower frequency (0·50 ± 0·85% of the total lymphocytes). Additionally, lymphopenia is frequently seen in SARS and influenza and in both diseases has been recognised as a negative predictor of outcomes.[1,2]. However, presence of atypical lymphocytes is not a laboratory feature of influenza.[3] The relative commonality of these cells compared to other viral infections, together with lymphopenia observed in many patients, may provide an important clue to further evaluate patients for COVID-19. Future studies in the characterisation of these cells could be helpful in our understanding of the pathophysiology of the disease.

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