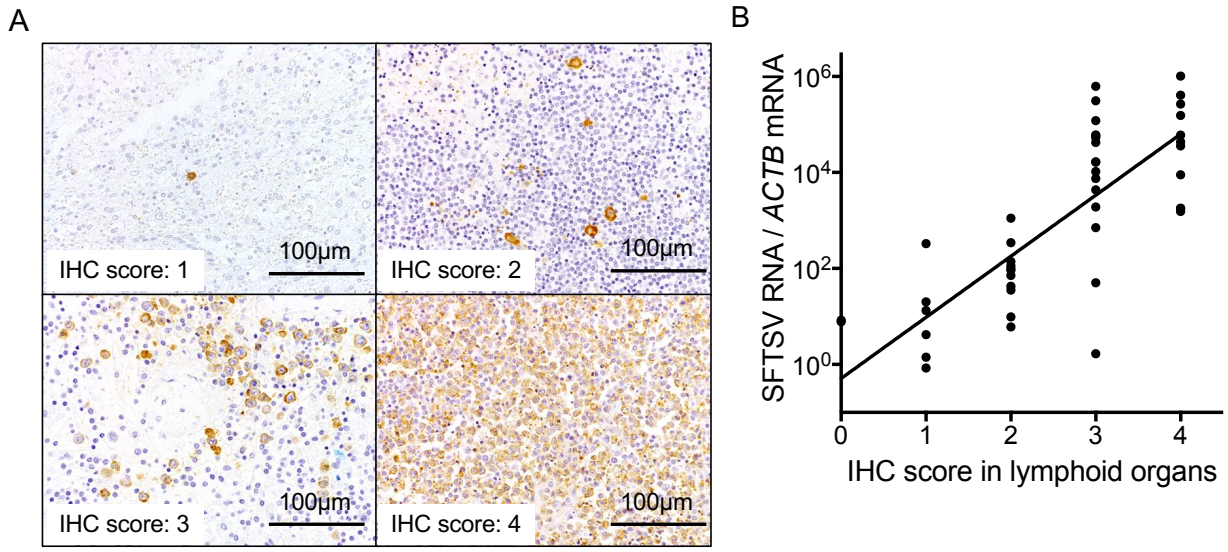
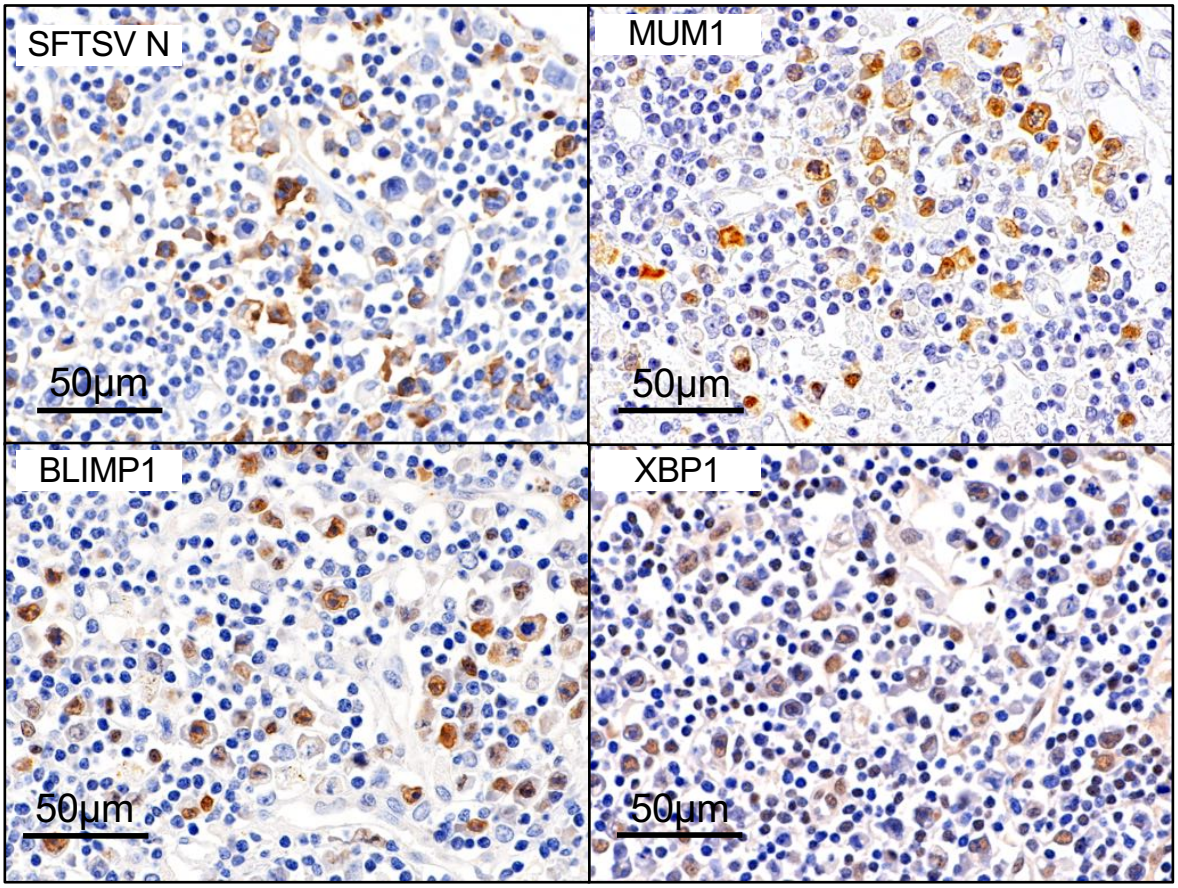
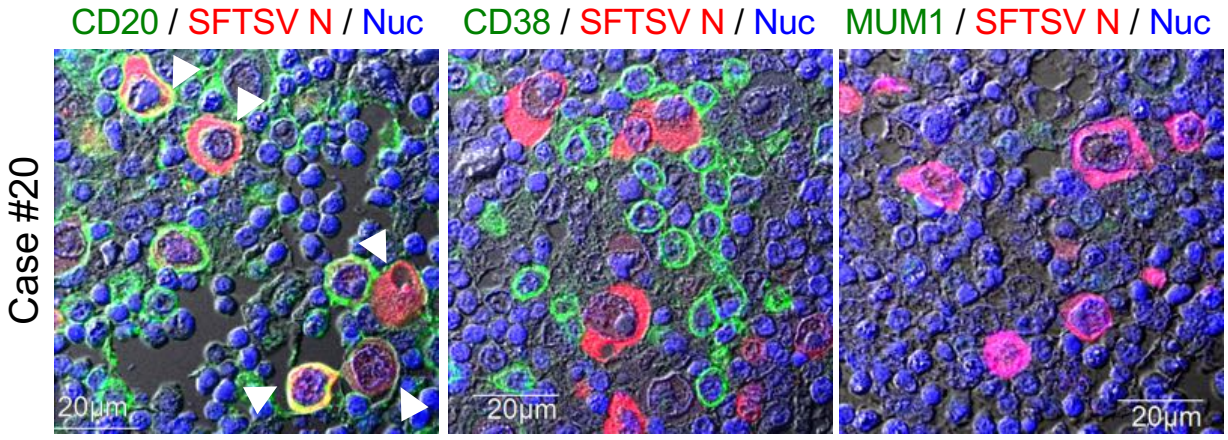


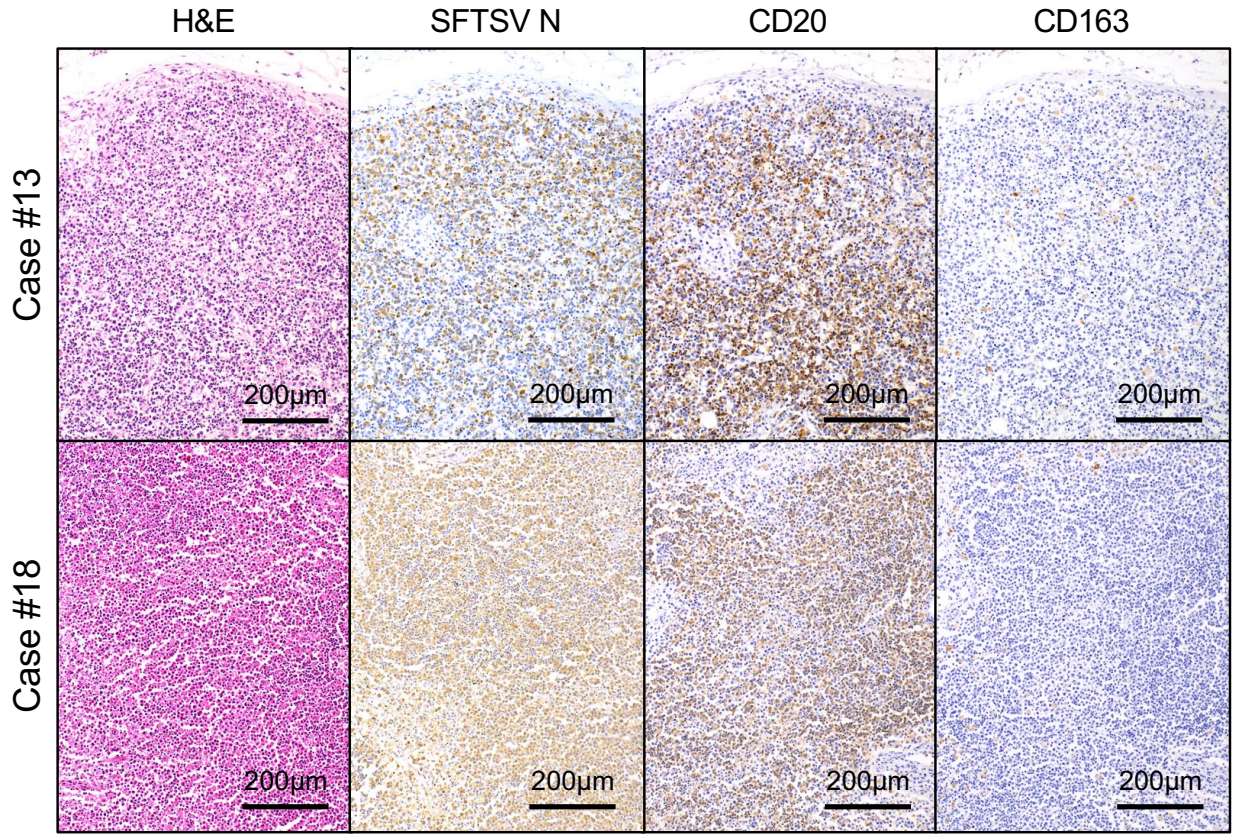
Supplemental Figure 1. SFTSV IHC scoring. (**A**) Representative IHC images for each SFTSV score. The number of SFTSV-positive cells in each section was estimated by the number of positive cells in areas with highest cellularity of positive cells in the section, according to the following criteria; Score 0: no positive cells in the section; Score 1: <5 positive cells per high-power field (HPF); Score 2: <50 positive cells per HPF; Score 3: <500 positive cells per HPF; Score 4: ≥500 positive cells per HPF. Scale bars, 100 μm. (B) Relationship between SFTSV IHC score and SFTSV RNA load in each tissue section. SFTSV RNA load in RNA extracted from serial sections was quantified to evaluate the reliability of SFTSV IHC scoring. Human ACTB mRNA was used as an internal reference gene for normalization of RNA extraction. The SFTSV RNA load was positively correlated with SFTSV IHC score in the lymphoid organs (Spearman's coefficient = 0.7814, p <0.0001).



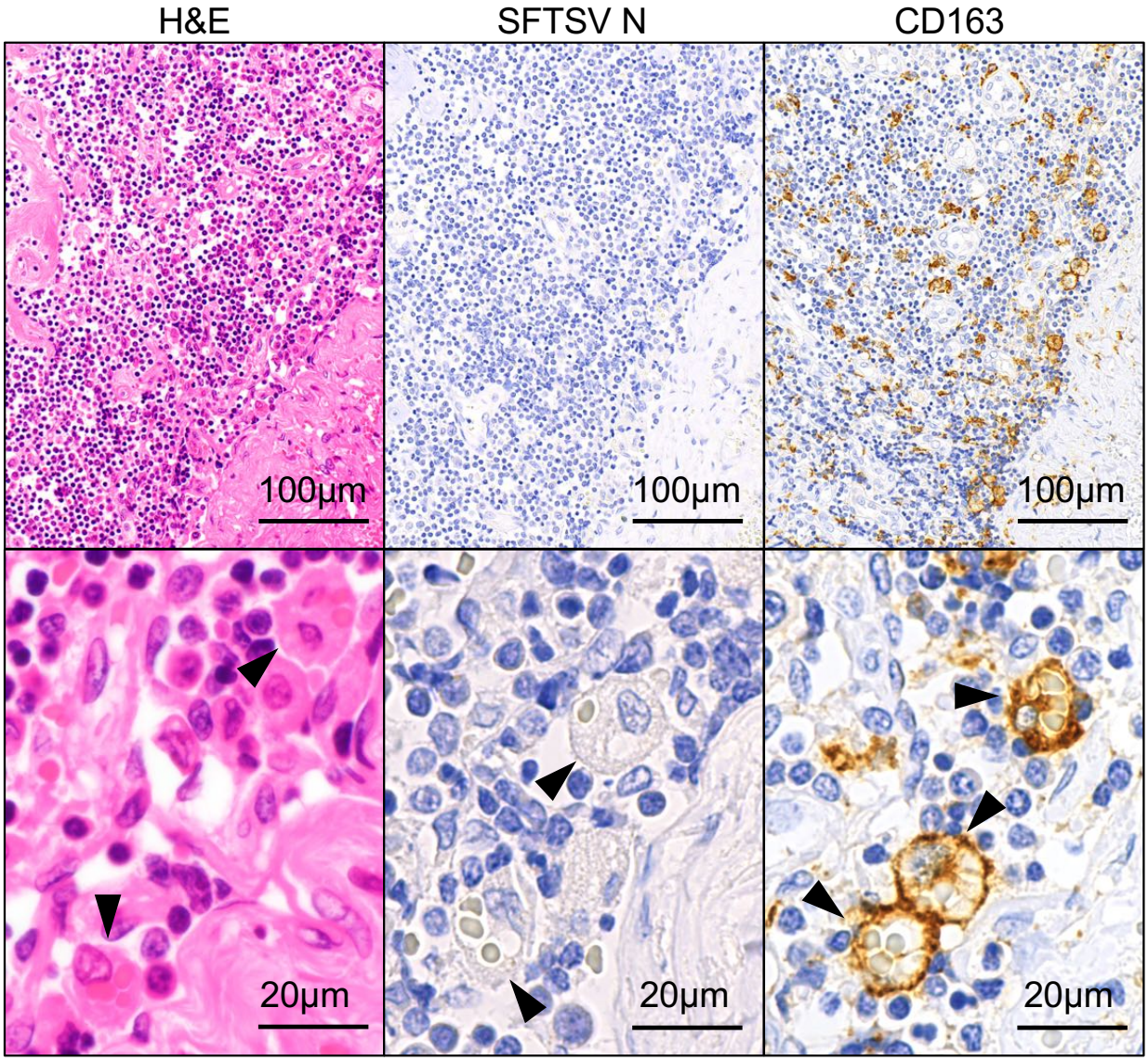
Supplemental Figure 2. Expression of essential transcription factors regulating plasmablast differentiation in lymph nodes of fatal SFTS. IHC images for SFTSV N, MUM1, BLIMP1, and XBP1 in an SFTSV-positive lymph node. Large atypical lymphocytes in the same area were positive for these transcription factors besides SFTSV antigen. Scale bars, 50 μm.



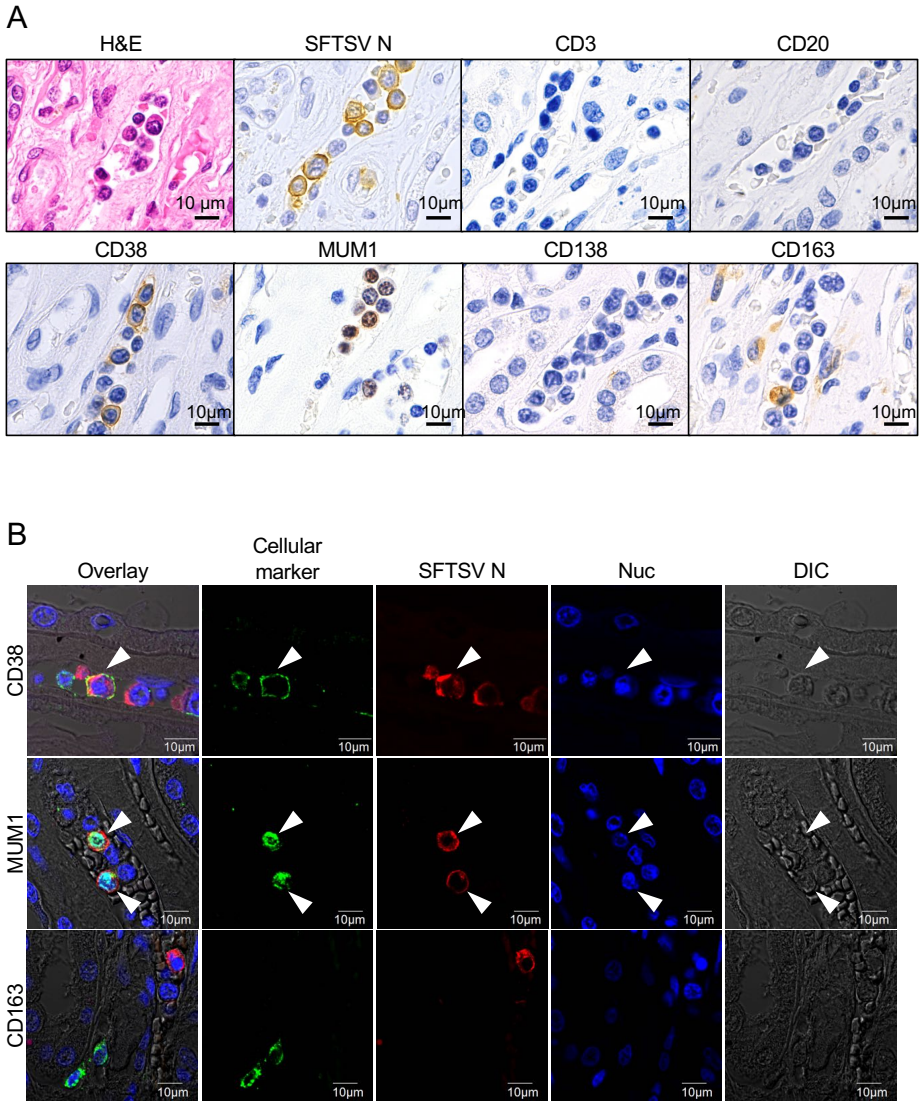
Supplemental Figure 3. Immunophenotype heterogeneity of SFTSV-susceptible B cells in fatal SFTS. Overlay images of immunofluorescence staining for TO-PRO-3 nucleic acid staining (Nuc, blue), SFTSV antigen (red), and immune-cell markers (green) in a lymph node section of Case #20 (Female, mid-fifties). SFTSV-positive cells were positive for CD20, but not for CD38 or MUM1. Scale bars, 20 μm. Arrowheads indicate colocalization of SFTSV and cell markers in the same cells.



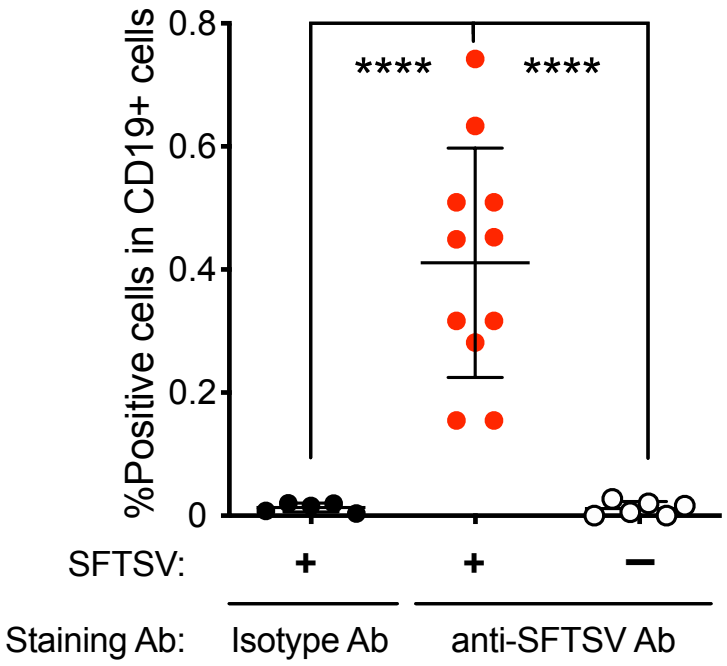
Supplemental Figure 4. Majority of SFTSV-antigen positive cells in the lymph nodes are B cells. H&E staining and IHC images for SFTSV N, B-cell (CD20) and macrophage (CD163) makers in a SFTSV-positive lymph node of Case #13 (Male, early-fifties), or Case #18 (Male, mid-sixties). Abundant B cells, but not macrophages, are shown in the area with numerous SFTSV-antigen staining. Scale bars, 200 μm.



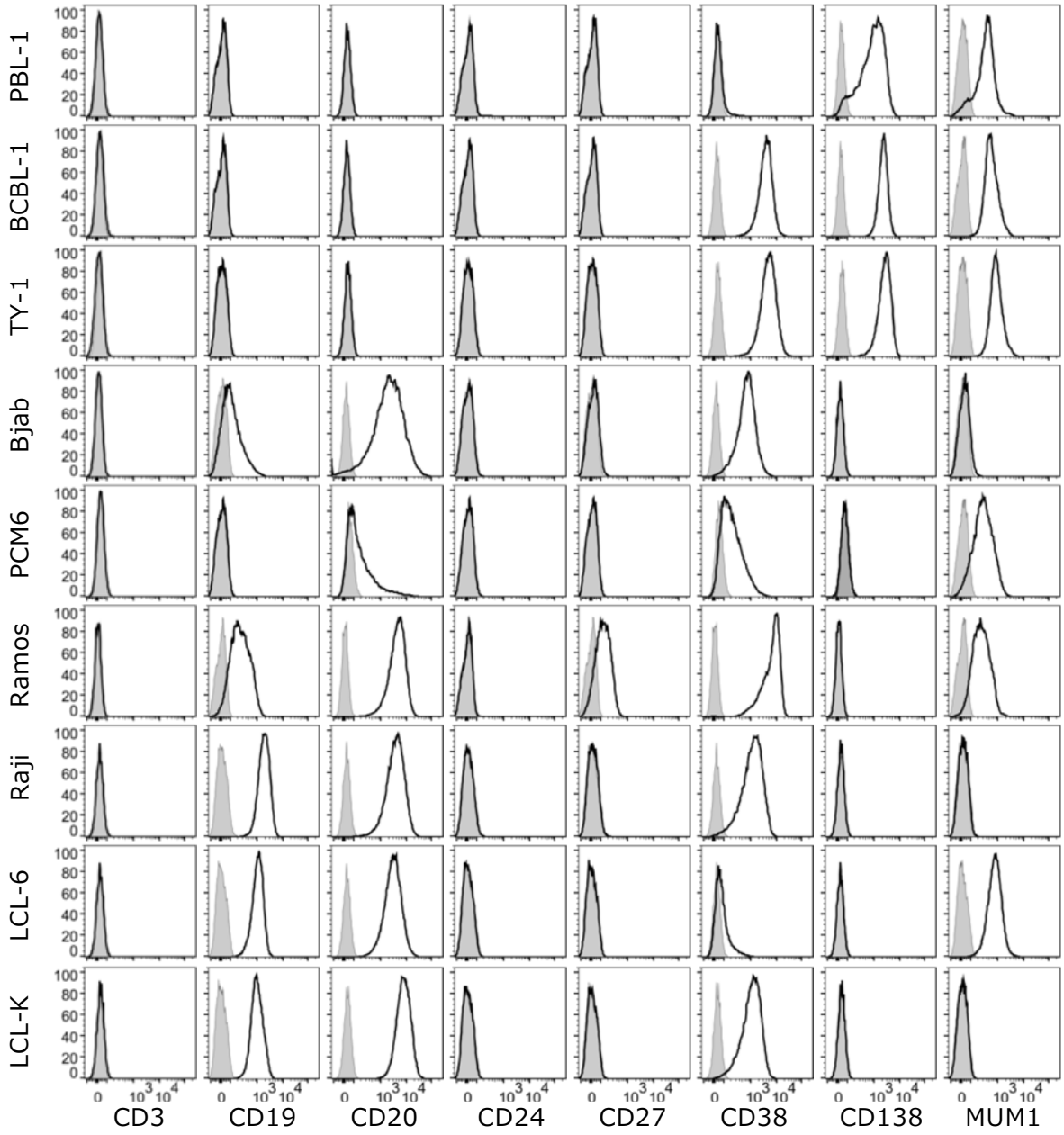
Supplemental Figure 5. Hemophagocytic macrophages in lymph nodes of fatal SFTS are not infected with SFTSV. H&E staining and IHC images for SFTSV N and a macrophages maker (CD163) in a SFTSV-negative lymph node of a fatal SFTS case (Case #3, female, early-eighties). Abundant CD163+ hemophagocytic macrophages (arrow heads) are shown in the lymph node without SFTSV-positive cells, which was obtained from the fatal SFTS case. Scale bars, 100 μm (upper panels), or 20 μm (lower panels).



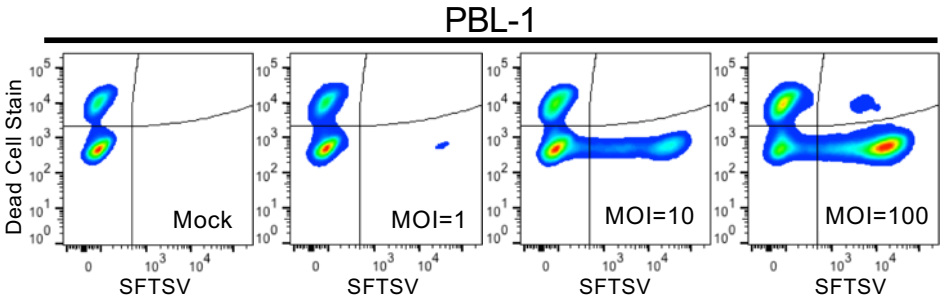
Supplemental Figure 6. SFTSV-infected mononuclear cells in the capillaries show plasmablastic differentiation. (A) H&E staining and IHC images for SFTSV N protein and immune-cell markers (CD3, CD20, CD38, MUM1, CD138, and CD163) of SFTSV-infected mononuclear cells in the capillary (renal medulla) in individuals who died from SFTS. The mononuclear cells in the capillary are stained with SFTSV N protein, CD38, MUM1, and CD163, but not CD3, CD20, or CD138. Scale bars, 10 μm. **(B)** Double IF staining for SFTSV N protein (red) and cellular markers (green, CD38, MUM1, or CD163) of mononuclear cells in the capillary. TO-PRO-3 nucleic acid staining (Nuc, blue), DIC and overlay images are also shown. Arrowheads indicate colocalization of SFTSV and cellular markers in the same cells. SFTSV-positive mononuclear cells in the capillaries were double-stained with cellular markers for plasmablasts (MUM1 and CD38), but not macrophages (CD163). Scale bars, 10 μm.



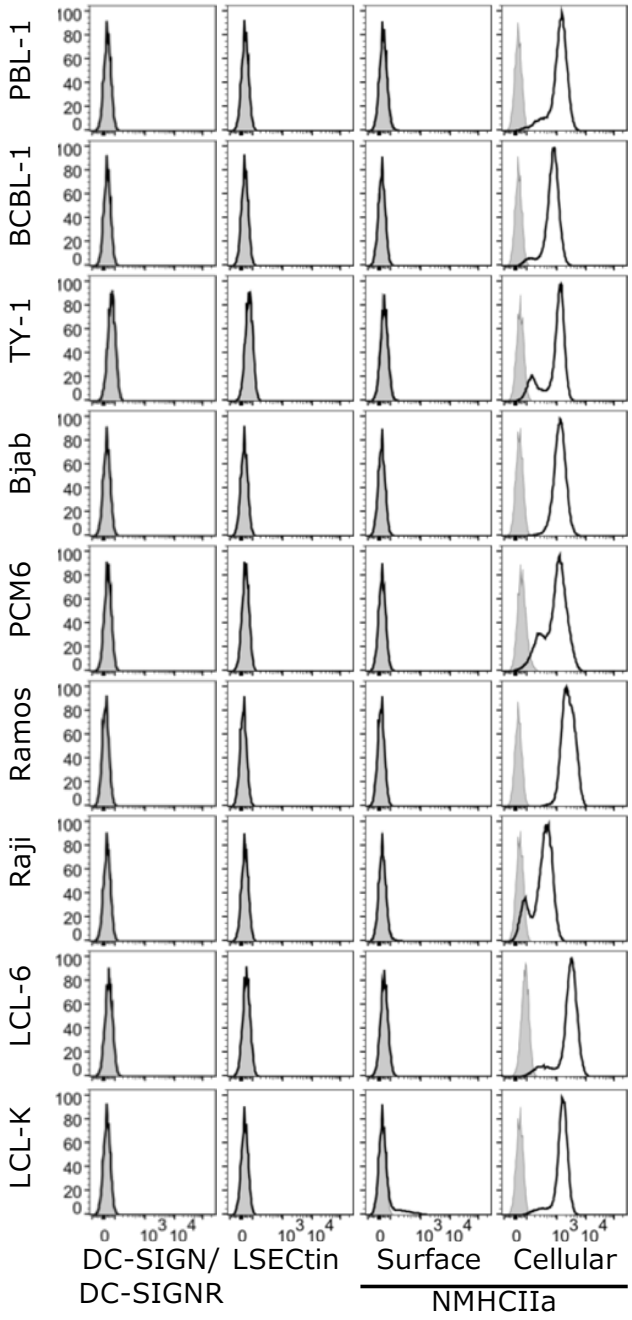
Supplemental Figure 7. Peripheral-blood B cells obtained from healthy adults are infected with SFTSV. The infectivity of SFTSV in CD19+ B-cell fraction was determined by intracellular staining with DyLight488-conjugated anti-SFTSV N antibody at 24 h post-inoculation. The specificity of this staining using DyLight488-conjugated anti-SFTSV N antibody was evaluated by staining of infected PBMCs with isotype control antibody (Isotype Ab) or uninfected PBMCs with DyLight488-conjugated anti-SFTSV N antibody (SFTSV－), in both of which minimal number of stained cells were detected (less than 0.03%), demonstrating that the stained cells (Mean = 0.41%) in CD19+ B-cell fraction are specific signals of SFTSV infected cells. Scatter plots also show mean ± SD. ****p <0.0001 (one-way ANOVA followed by Holm–Sidak's multiple-comparisons test).



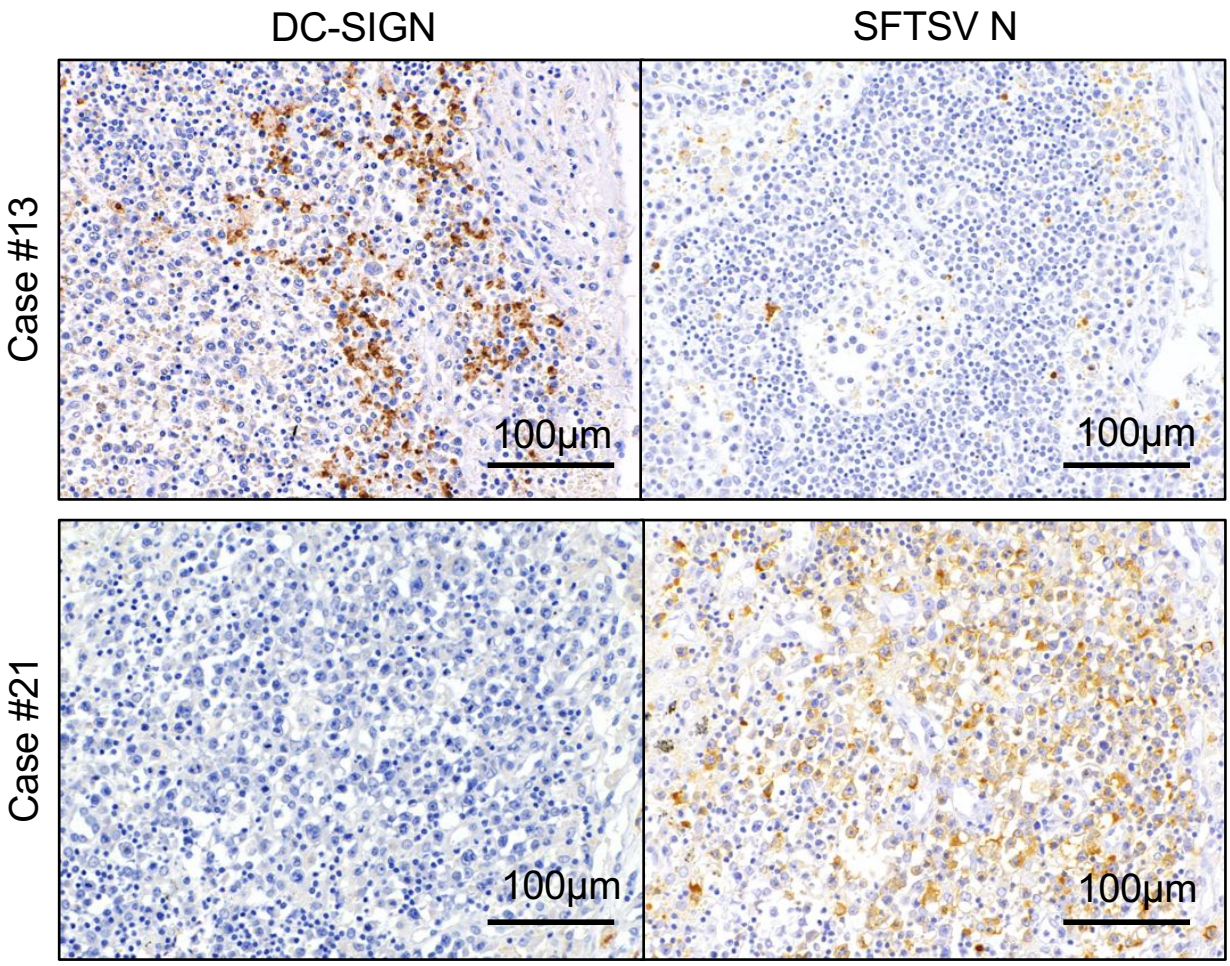
Supplemental Figure 8. Immunophenotypes of human B cell lines. Expression of cell markers in nine human B cell lines derived from B cell malignancies was examined by flow cytometry. For markers other than MUM1, unfixed cells were stained with antibodies for examination of cell-surface expression. For MUM1 expression, cells were fixed and permeabilized before staining to detect intracellular molecules.



Supplemental Figure 9. Quantitative evaluation of SFTSV susceptibility of PBL-1 cells. PBL-1 cells were inoculated with SFTSV (MOI = 1, 10, 100), incubated for 24 h, then subjected to flow cytometry with DyLight488-labeled anti-SFTSV nucleocapsid protein (N) antibody. SFTSV infection of PBL-1 cells required a high viral MOI.



Supplemental Figure 10. Expression of SFTSV-receptors in human B cell lines. Expression of reported SFTSV receptors DC-SIGN/DC-SIGNR, LSECtin, and NMHCIIa in human B cell lines was examined by flow cytometry. Both cell-surface (Surface) and intracellular (Cellular) expression of NMHCIIa were examined. None of the human B cell lines expressed any of the reported SFTSV receptors on the cell surface, although intracellular NMHCIIa was expressed at various levels in all of the cell lines.



Supplemental Figure 11. SFTSV-infected cells in the lymph nodes in fatal SFTS do not express DC-SIGN. IHC staining for DC-SIGN, which is one of the reported SFTSV receptors, was performed in SFTSV-positive lymph nodes from two fatal cases (Case #13, male, early fifties; Case #21, male, late sixties). Expression of DC-SIGN was not correlated with SFTSV N immunostaining, suggesting that DC-SIGN did not act as a viral receptor in the lymph nodes of individuals who died as a result of SFTS. Scale bars, 100 μm.