HHS Public Access

Author manuscript

Lancet Haematol. Author manuscript; available in PMC 2021 March 22.

Published in final edited form as:

Lancet Haematol. 2020 March ; 7(3): e238–e246. doi:10.1016/S2352-3026(19)30206-6.

Myelodysplastic syndrome and acute myeloid leukemia in patients with Shwachman Diamond syndrome: a multicentre, retrospective, cohort study

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Conflicts of interest: None

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Abstract

Background: Data to inform surveillance and treatment for leukemia predisposition syndromes are limited and recommendations largely based on expert opinion. This study aimed to investigate the clinical features and outcomes of myelodysplastic syndrome and acute myeloid leukemia in Shwachman Diamond syndrome, an inherited marrow failure disorder with high risk of myeloid malignancy.

Methods: We performed a multicentre, retrospective cohort study in 17 centres in the USA and Canada. Patients with a genetic or clinical diagnosis of Shwachman Diamond syndrome who developed myelodysplastic syndrome or acute myeloid leukemia were eligible without additional restriction. Medical records from March 1, 2001 to October 5, 2017 were reviewed for 36 patients. Blinded central review of bone marrow pathology was performed in 27 available cases. Description of clinical features and survival assessment was performed. Median follow-up was 4·9 years (range: 0.3–10.1, IQR: 3.9–8.4).

Findings: Median age was 18 years (range: 0.5–47.0, IQR:10–24). Central pathology review concurred with local diagnosis in 56% (n=15/27). Treatment was heterogeneous with 10 chemotherapy regimens and 16 hematopoietic stem cell transplant regimens. Only 1 of 10 initially treated with chemotherapy for leukemia achieved complete remission. Median survival from myelodysplastic syndrome / leukemia diagnosis was 0·99 years in leukemia (95% CI: 0.2–2.4, IQR: 0.6–1.1) and 7·7 years in myelodysplastic syndrome (95% CI: 0.8-NA; IQR: 0.7-NA). Overall survival at 3 years was 11% (95% CI:1–39, n=10) and 51% (95% CI:29–68, n=26) for leukemia and myelodysplastic syndrome respectively. Bone marrow surveillance was conducted in 33% (n=3/9) of leukemia and 46% (n=11/24) of myelodysplastic syndrome subjects. Individuals

monitored with bone marrow surveillance prior to myelodysplastic syndrome / leukemia diagnosis had a 3-year OS of 62% (95% CI: 32–82, n=14) compared with 28% without surveillance (95% CI:10–50, n=19) (p=0·13). Several patients developed myelodysplastic syndrome in the setting of stable blood counts (n=6).

Interpretation: Prognosis is poor for Shwachman Diamond syndrome patients with leukemia due to both therapy-resistant disease and treatment-related toxicities. Improved surveillance algorithms for early disease detection/risk stratification, biological studies of clonal evolution and prospective clinical trials are needed to inform effective prevention and treatment strategies for leukemia predisposition.

INTRODUCTION

Shwachman Diamond syndrome is an autosomal recessive disorder characterized by bone marrow failure, exocrine pancreatic dysfunction, and predisposition to myelodysplasia and acute myeloid leukemia (1). Over 90% of patients with Shwachman Diamond syndrome carry biallelic mutations in the Shwachman-Bodian-Diamond syndrome (*SBDS*) gene on chromosome 7q11, encoding a protein involved in ribosomal maturation. (2,3) Patients with mutations in *SRP54*, *DNAJC21*, and *EFL1* may present with clinical features of Shwachman Diamond syndrome. (4)

Myelodysplastic syndrome and acute myeloid leukemia are major life-threatening complications of Shwachman Diamond syndrome. Reported rates of malignant transformation range between 5–36%, and Shwachman Diamond syndrome may be unrecognized in young adults with myeloid malignancy. A Center for International Blood and Bone Marrow Transplant Research study found that 4% of young patients undergoing hematopoietic stem cell transplantation (HSCT) for myelodysplastic syndrome had Shwachman Diamond syndrome. (5)

Baseline marrow dysmorphologies make the diagnosis of myelodysplastic syndrome and acute myeloid leukemia challenging in leukemia predisposition disorders. (1,6) Recent revisions in WHO definitions of myelodysplastic syndrome and acute myeloid leukemia warrant reassessment of myelodysplastic syndrome or acute myeloid leukemia outcomes in Shwachman Diamond syndrome using current diagnostic criteria.

There is currently no consensus regarding treatment, including the role of pre-HSCT cytoreductive chemotherapy or recommended conditioning regimens for HSCT for Shwachman Diamond syndrome patients. Data are sparse, coming from case reports and small case series. (7,8) Although myelodysplastic syndrome and acute myeloid leukemia are now recognized to be clinically and biologically distinct, prior studies often reported combined outcomes of both diagnoses together. (4)

We conducted a multi-institutional retrospective study of patients with Shwachman Diamond syndrome and myelodysplastic syndrome or acute myeloid leukemia. We describe demographics, disease characteristics, challenges of pathologic diagnosis, surveillance practices, therapy response, and overall survival. These data are critical to inform medical management of this leukemia-predisposition syndrome.

METHODS

Study Design:

This study was approved by Cincinnati Children's Hospital IRB (primary IRB) and local IRBs. Retrospective chart review was performed at 17 institutions in collaboration with the North American Shwachman Diamond Syndrome Registry. Inclusion criteria consisted of 1) either biallelic mutations in the *SBDS* gene or a clinical diagnosis of Shwachman Diamond syndrome as defined by cytopenias and pancreatic dysfunction, (9) and 2) diagnosis of myelodysplastic syndrome or acute myeloid leukemia. All slides and data extracted from the medical record were de-identified and collected in the Research Electronic Data Capture (REDCap) system. (10) Treatment response criteria were reported as determined by local treating physicians. Serial bone marrow surveillance was defined as bone marrow examinations performed routinely in the absence of symptoms.

Pathology Review:

Blinded centralized pathology review following current WHO 2016 diagnostic criteria was performed by two independent groups of pathologists with expertise in marrow failure syndromes in the 27 subjects with available slides.(11) If central review indicated a different diagnosis from the local report, subjects were reclassified accordingly for further analysis. One patient with a local diagnosis of myelodysplastic syndrome was excluded from further analyses after determination of marrow morphology within the normative baseline of Shwachman Diamond syndrome and no cytogenetic abnormalities (Appendix p7). Data from the remaining 36 patients are reported.

Statistical Analysis:

Summary statistics are reported for continuous variables (mean, standard deviation, median, range) and binary variables (proportions and exact binomial 95% confidence intervals). Fisher's exact test was used to compare categorical outcomes. Survival time was defined as time from initial diagnosis (acute myeloid leukemia, myelodysplastic syndrome, myelodysplastic syndrome excess blasts (EB) 1/2) to death or date of last follow-up. Survival was estimated using Kaplan-Meier method and compared using the log-rank test. In the analysis summarizing outcomes by central review diagnosis, the local diagnosis is used if slides were not available for review.

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author oversaw the study and the final responsibility to submit for publication.

RESULTS

The cohort included 36 Shwachman Diamond syndrome individuals with myelodysplastic syndrome or acute myeloid leukemia. Patient demographics and disease characteristics are shown in Table 1 and Appendix (p5–8). Median year of diagnosis was 2010 (range 2001–2017; IQR: 2007–2013), and median follow-up was 4.9 years (95%CI: 3.9–8.4, IQR: 3.9–8.4). Data were collected from clinical records dating between March 1, 2001 to October 5,

2017. The diagnosis of Shwachman Diamond syndrome was established by presence of biallelic *SBDS* mutations (n=30) (Appendix p3–4) or clinical diagnosis of cytopenias and exocrine pancreatic dysfunction (n=6). Among the 27 patients with slides available, central pathology review agreed with local review in 56% (n=15/27) (CI: 35–75) (Appendix p9). The most common discrepancy was the distinction between low grade myelodysplastic syndrome versus advanced myelodysplastic syndrome with excess blasts. This highlights the challenges of enumerating blasts in a hypocellular marrow with baseline dysmorphologies.

Initial diagnosis and age at presentation are show in Table 2. G-CSF use at time of malignancy diagnosis was noted for 35% (n=9/26) and 10%(n=1/10) of myelodysplastic syndrome and leukemia cases respectively, which is similar to the North American Shwachman Diamond syndrome registry 45% (n=45/99) of patients with biallelic SBDS mutations . Complex karyotypes, defined by three or more numerical and/or structural chromosomal abnormalities, were seen in 36% (n=8/22) and 80% (n=8/10) of myelodysplastic syndrome and leukemia cases (p=0·05), respectively.

Surveillance marrow exams showed predominantly hypocellular marrows with frequent mild dyspoiesis of myeloid, erythroid, and/or megakaryocytic lineages. Baseline morphologic atypia in surveillance samples was most pronounced in the myeloid lineage, where mature neutrophils often had a combination of incomplete nuclear segmentation and variable hypogranulation (Appendix p1). These features fall within the spectrum of baseline Shwachman Diamond syndrome marrow morphology.

Patients with myelodysplastic syndrome demonstrated subtle but progressively more pronounced lineage dysplasias. Dysmorphic features in the myeloid lineage predominated in myelodysplastic syndrome and included prominent nuclear hypolobation (“Pelger-Huet”-like forms), prominent cytoplasmic hypogranulation, and cases with markedly enlarged myeloid precursors and forms with prominent basophilic cytoplasm. Most cases of myelodysplastic syndrome also had more significant dyserythropoiesis.

The baseline dysmorphologies noted in all Shwachman Diamond syndrome marrows pose a major challenge for the morphologic diagnosis of myelodysplastic syndrome. In particular, the late granulocyte precursors and mature granulocytes often have hyposegmented nuclei and may be hypogranular. Dysplasia in the erythroid lineage at baseline in Shwachman Diamond syndrome is unusual, and, particularly when combined with a progressively increasingly cellular marrow is concerning for myelodysplastic syndrome, even in the absence of cytogenetic abnormalities. This pattern differs from the prototypical sporadic myelodysplastic syndrome in older adults using WHO guidelines. However, leukemia may evolve without apparent antecedent dysplasia or cytogenetic abnormalities. We did not observe a correlation between blast count and severity of dysplasia for myelodysplastic syndrome.

Thirty of 34 subjects (88%) with available treatment data received treatment. Treatments were heterogeneous (Appendix p5–8). Ten different initial chemotherapy regimens, including hypomethylating agents (n=2) and cytoreductive chemotherapy (n=8), were delivered. HSCT was initial therapy for 16 patients. Sixteen different HSCT approaches

were reported, including 13 reduced intensity and 3 myeloablative conditioning regimens (Appendix p5–8).

Patients with leukemia had a median time to first treatment of 0·3 months (range: 1 day-4·4 months; IQR: 2 days - 0.9 months) versus 4·7 months (range 1·1–28·9; IQR: 2.7–6.6) for myelodysplastic syndrome. However, median time to HSCT was similar with 4·6 months (range 0·9– 6·1; IQR: 2.9–5.6) for leukemia, and 4·7 months (range 1·1–28·9; IQR: 3.0–7.3) for myelodysplastic syndrome.

Eighteen of 26 subjects diagnosed with low grade or high grade myelodysplastic syndrome received therapy for myelodysplastic syndrome consisting of either upfront HSCT (n=14) or upfront chemotherapy (n=4). Of the 14 who received upfront HSCT, 10 (71%; 95% CI: 41·9–91·6) achieved a complete response (CR) following HSCT of which 7 remain alive with with median follow-up of 82 months from diagnosis (range 39–120 months; IQR: 59–94), 2 died in remission of treatment-related toxicities 4 and 6 months post-HSCT, and 1 died with recurrent disease 9 months post-HSCT. Three patients with myelodysplastic syndrome who underwent upfront HSCT developed graft failure, of whom 2 died with active disease at 19 and 26 months and 1 died with unknown disease status at 18 months. One patient is alive at 39 months, response to therapy unknown. Only one of four patients with myelodysplastic syndrome who received upfront chemotherapy achieved a CR. Of this group, 1 subsequently underwent HSCT and died at 4 months of multi-organ failure, 2 died at 4 and 7 months of infection and disease, and one continues on a hypomethylating agent with active disease at 56 months. Four myelodysplastic syndrome subjects received no therapy, 2 died with active disease at 2 and 92 months, and 2 were lost to follow-up with active disease at 18 and 121 months. Two subjects did not have treatment data available and were lost to follow-up at 18 and 21 months. Two subjects with an initial diagnosis of myelodysplastic syndrome EB1/2 progressed to leukemia at 2·5 and 3·8 months prior to receiving any myelodysplastic syndrome-directed therapy.

Twelve patients were treated for leukemia, including 2 myelodysplastic syndrome-EB1/2 subjects who progressed to leukemia. Eighty-three percent (10/12) received pre-HSCT therapy (hypomethylating agent = 2, cytoreductive chemotherapy =8) with intent to proceed with HSCT; only 1 (95% CI: 0·3–44·5) achieved CR. The only patient with normal cytogenetics at initial leukemia diagnosis was also the only patient who achieved CR following chemotherapy. This subject remains alive 49 months from diagnosis following a complicated post-HSCT course, including 2 episodes of graft failure requiring a total of three transplants. The other subjects who received upfront pre-HSCT therapy (n=9) died with median survival of 9 months (range 1–29 months; IQR:4–13). Two leukemia subjects received HSCT as initial therapy; 1 achieved CR but died of treatment-related complications in remission at 9 months. The other progressed from myelodysplastic syndrome-EB1/2 to leukemia and underwent HSCT without prior cytoreductive chemotherapy and remains alive without disease at 6 months.

Three-year OS from initial leukemia diagnosis was 11% (95% CI: 1–39) with median survival of 0.99 years (95% CI: 0.2–2.4; IQR: 0.6–1.1) and median follow up of 4·1 years (95% CI: 0.3-NA, IQR: 0.3-NA) (Figure 1A). Three-year OS for myelodysplastic syndrome

was 51% (95% CI 29–68), with median survival of 7·7 years (95% CI: 0.8-NA, IQR: 0.7-NA) and median follow-up of 5·1 years (95% CI: 3.3–8.4; IQR: 3.3–8.4) (Figure 1B). OS analysis separating low-risk and high-risk myelodysplastic syndrome are shown in Appendix p2. When restricted to subjects with central pathology review, three-year estimated overall survival was 20% for leukemia (n=5; 95% CI: 1–58%) and 45% for myelodysplastic syndrome (n=21; 95% CI:22–65%). No effect of age on overall survival was detected within diagnoses with a hazard ratio of 1.03 for leukemia (95% CI:0.98–1.08, p=0.35) and 1.03 for myelodysplastic syndrome (95% CI:0.99–1.08,p=0.11). No difference in overall survival was detected by year of diagnosis (HR=1.0, 95% CI:0.9–1.2, p=0.57) or treatment (HR=1.0, 95% CI:0.9–1.1, p=0.83) using Cox proportional hazards model (p>0.50).

Eighty percent (n=8/10) of those with leukemia compared to 36% (n=8/22) with myelodysplastic syndrome had complex cytogenetics (p=0·05). Subjects with myelodysplastic syndrome with complex karyotype (n=22) had a 3-year OS of 15% (1,47) compared with 64% (34, 83) in those without complex karyotype, (p=0·15)(Figure 2A).

Thirty-three of 36 (8/10 leukemia, 4/5 myelodysplastic syndrome-EB1/2, 21/21 myelodysplastic syndrome) were known to have Shwachman Diamond syndrome prior to development of malignancy. Serial bone marrow surveillance was performed for 14 subjects (9 with myelodysplastic syndrome, 2 with myelodysplastic syndrome-EB1/2, 3 with leukemia). Nineteen did not receive bone marrow surveillance, and 3 had unknown surveillance status.

Median follow-up was similar in no surveillance (n=19) and surveillance (n=14) cohorts at 4·7 (95% CI: 1.5-NA; IQR: 1.5-NA) and 6·5 years (95% CI: 3.3-NA, IQR: 3.3-NA), respectively (p=0·79). We observed median overall survival of 1·1 (95% CI: 0.6-NA; IQR:0.6-NA) vs. 7.7 years (95% CI: 0.6-NA, IQR:1.1-NA) and 3-year overall survival estimates of 28% (95% CI: 10–50) vs. 62% (95% CI: 32–82) for the group without vs with marrow surveillance(p=0.13) (Figure 2B), suggesting need for further evaluation. Median age at malignancy diagnosis was 11·9 (range 0·5–45 years; IQR: 5.6–19.8) and 19 (range 1·4 –47 years; IQR:14.4–31.5) years for surveillance versus no-surveillance, respectively (p=0·13).

There was lack of uniformity in the specific marrow surveillance tests performed, even within subjects. No subjects had flow cytometry, FISH, and karyotype performed on all surveillance marrows. Flow cytometry, FISH, and karyotype were sent on 49% (n=43), 72% (n=63), and 53% (n=46), respectively of the 87 surveillance marrows. Del20q was present in 3 cases prior to diagnosis (1 leukemia, 1 myelodysplastic syndrome-EB1/2, 1 myelodysplastic syndrome), and iso7q was present in 1 case of myelodysplastic syndrome-EB1/2 and 1 case of myelodysplastic syndrome prior to diagnosis. Monosomy 7 was detected intermittently by FISH at levels below clinical thresholds for several years prior to diagnosis in one case each of leukemia and myelodysplastic syndrome. One case of myelodysplastic syndrome had del5q present prior to diagnosis, and another case of myelodysplastic syndrome had low levels of del7q and trisomy 8 detected by FISH in several marrows preceding diagnosis. However, karyotypes and FISH were not routinely sent on all surveillance marrows and therefore trends were difficult to determine.

Of the 14 patients with marrow surveillance, there was no clinical concern for myeloid malignancy in 4 prior to the diagnostic marrow showing myelodysplastic syndrome (n=3), myelodysplastic syndrome EB1/2 (n=1). One patient was noted to have a CBC abnormality on the day of surveillance marrow which showed leukemia. Two patients had no available clinical reports to assess suspicion prior to marrow exam.

Eight of 14 receiving marrow surveillance had antecedent marrow abnormalities, typically worsening dysplasia prior to diagnosis of myelodysplastic syndrome (n=5), myelodysplastic syndrome-EB1/2 (n=1), and leukemia (n=2). One patient had warning signs with increasing dysplasia noted on 2 separate marrows (1 year and 6 months) and decreasing ANC on G-CSF prior to presenting with leukemia, illustrating the need to proceed rapidly to transplant. Six patients with marrow surveillance had no prior marrow abnormalities leading up to diagnosis of myelodysplastic syndrome (N=3), myelodysplastic syndrome-EB1/2 (n=1) or leukemia (n=1), but three of these developed peripheral cytopenias leading up to the diagnostic marrow.

Six of 10 patients presenting with leukemia did not have surveillance and surveillance status was unknown for one. Although surveillance could identify actionable changes prior to progression to leukemia, the presentation of one patient with leukemia without an apparent antecedent dysplastic phase or cytogenetic abnormalities highlights the limitations of current surveillance tools and the need for better biomarkers for risk stratification. Fifteen cases with longitudinal CBC data prior to diagnosis of malignancy were reviewed (4 leukemia, 2 myelodysplastic syndrome-EB1/2, 9 myelodysplastic syndrome). Six had only mild cytopenias prior to diagnosis of myelodysplastic syndrome or leukemia. Two had stable and 4 had fluctuating blood counts. The lack of progressive changes in blood counts did not preclude marrow disease, suggesting that CBC surveillance alone may be less sensitive than combined CBC/marrow surveillance. The MCV was stable or decreasing in 2/4 cases of leukemia, decreasing in 2/2 cases of myelodysplastic syndrome-EB1/2, decreasing in 3/9 myelodysplastic syndrome cases and stable in 4/9 myelodysplastic syndrome cases.

Discussion

This multi-institutional retrospective study reports clinical features and outcomes of the largest cohort of Shwachman Diamond syndrome patients with myelodysplastic syndrome and acute myeloid leukemia reported to date to our knowledge. Evolution of diagnostic criteria for myelodysplastic syndrome and leukemia renders prior studies of Shwachman Diamond syndrome difficult to extrapolate to current practice, so central pathology review was performed using present-day standards. Overall survival from myelodysplastic syndrome in our cohort was lower than expected for myelodysplastic syndrome in the absence of Shwachman Diamond syndrome, and markedly lower in those with leukemia (11% 3-year OS) compared with around 50% 5-year OS in young adults in the absence of Shwachman Diamond syndrome. (12) Treatment failure was due to both toxicity of therapy and resistant disease indicating need for novel approaches.

Central pathology review highlighted complexities in the diagnosis of myelodysplastic syndrome and leukemia in Shwachman Diamond Syndrome. Myelodysplastic syndrome

poses diagnostic challenges even in the non-Shwachman Diamond syndrome population, with significant inter-observer variability in determination of dysplasia.(13–16) . Quantitation of blasts in a hypocellular marrow yielded discrepancies between blast enumeration within the biopsy, versus aspirate or flow cytometry where dilution with blood could be problematic (17–24) . Analysis of aberrant antigen expression that may be seen in myelodysplastic syndrome was not available. Diagnosis after central pathology review differed from local diagnosis in 44% of cases with available slides, perhaps because of morphology challenges and revisions in WHO criteria for myelodysplastic syndrome/ leukemia (11) . These data emphasize the value of enlisting the expertise of a hematopathologist experienced with Shwachman Diamond syndrome.

Standard chemotherapy approaches to leukemia led to poor overall survival. Many patients were unable to proceed to HSCT due to disease progression or mortality with chemotherapy. Pre-HSCT cytoreductive chemotherapy for leukemia in Shwachman Diamond syndrome failed to prevent relapse and carried unacceptably high toxicity. Further clinical and biological studies are needed to determine whether standard WHO definitions of acute myeloid leukemia based on percentage of blasts inform the need for future novel cytoreductive therapy for patients with Shwachman Diamond syndrome. New therapeutic strategies to achieve remission are needed in a bone marrow failure syndrome with poor stem cell reserve and high end-organ toxicities. The role of standard pre-HSCT cytoreductive chemotherapy approaches has also been questioned for Fanconi Anemia, another marrow failure and cancer predisposition syndrome, and for patients with either germline or somatic *TP53* mutations, who tend to respond poorly to cytotoxic agents but have had some response to hypomethylating agents, especially when combined with venetoclax. (25–28)

Surveillance and management of patients with in clinical practice was highly variable. Only a subset of patients with Shwachman Diamond syndrome were being monitored, and there was marked variability in surveillance testing, even for a given patient over time. The Shwachman Diamond syndrome draft consensus guidelines recommend marrow surveillance based on expert opinion (9) ; however, published data are sparse regarding the benefit of marrow surveillance on overall survival of patients with leukemia predisposition. At three years, the proportion of subjects alive in our study was 28% (95% CI: 10–50) for those without marrow surveillance and 62% years with marrow surveillance (95% CI: 32–82). Patients compliant with surveillance might also be more compliant with other aspects of care, contributing to improved outcomes. Comprehensive centralized prospective collection of data is essential to develop evidence-based surveillance strategies for leukemia predisposition disorders. IPSS-R and WPSS have not been validated in patients with myelodysplastic syndrome arising from inherited marrow failure syndromes

Review of complete blood counts (CBC) prior to presentation with myelodysplastic syndrome or leukemia revealed limitations of CBC surveillance alone for early disease detection. CBCs were stable or even normal in some patients with cytogenetic and morphologic evolution to myelodysplastic syndrome in bone marrow. MCV trend was also not a consistent indicator of evolving myeloid malignancy in this cohort, and caution is advised in relying on the MCV for monitoring.

This study was limited by its retrospective nature and resulting lack of complete central pathology review, molecular analysis of for clonal evolution or comparator group of SDS patients without MDS or AML. Currently, numbers are too small to draw conclusions regarding risks of hematologic malignancy based on specific germline *SBDS* mutations. Similarly, this study was not designed to determine the effect of specific patient characteristics, such as G-CSF treatment prior to the development of myelodysplastic syndrome or leukemia. Chronic G-CSF treatment may allow patients to live longer thus extending the time frame that they are at risk of developing a malignancy, or individuals with severe disease and highest malignancy risk might require higher doses of G-CSF. (29)

Although we found that surveillance can capture early actionable abnormalities identifying patients at high risk for progression to acute myeloid leukemia, leukemia may also develop without antecedent warning discernable with currently available surveillance testing. Additional risk stratification strategies are under investigation in a prospective cohort. Somatic clonal abnormalities have been noted at young ages outside the context of myelodysplastic syndrome/leukemia in patients with germline genetic predisposition to myeloid malignancies. (28) Prior studies have shown that TP53 mutations are common in Shwachman Diamond syndrome, with or without myelodysplastic syndrome, so it is currently unclear whether isolated *TP53* mutations constitute an actionable finding.(5,30) It has been hypothesized that *TP53* mutations arise from selective pressures resulting from a failing marrow, and may be initiating events mediating disease progression to myeloid malignancies. Although somatic mutation analysis (including *TP53 a*nalysis) is now available clinically, it is not yet clear how to utilize this information to inform the treatment plan. Longitudinal studies of clonal evolution with respect to clinical outcomes are needed. A prospective centralized registry-based approach is essential to improve outcomes of patients with rare diseases by identifying patients at risk and systematically collecting clinical data and annotated samples for ongoing biological studies to inform therapeutic decisions. The poor prognosis of acute myeloid leukemia, and to a lesser extent myelodysplastic syndrome, documented in this study provides a compelling rationale for prospective studies to evaluate the effect of early intervention based on surveillance data on overall survival. Novel therapies with both decreased toxicity and improved anti-leukemic properties are urgently needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

This work was supported by NIH/NIDDK R24 DK099808 and NCRR/NIH UL1-RR026314-01 (Redcap), NIH T32 HL007574-36 (E.F.) and in part by the Intramural Research Program of the NIH and the National Cancer Institute (B.P.A., L.J.M.). One of the patients from Seattle/Fred Hutchinson Cancer Research Center was enrolled in a clinical trial supported in part by the NIH (grant PO1 HL122173) The authors gratefully acknowledge Dr. David Steensma for critical review of the manuscript.

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Research in Context

Evidence before this study

We searched Ovid and PubMed with the terms “myelodysplastic syndrome”, “acute myeloid leukemia,” “treatment,” “leukemia predisposition,” and “shwachman diamond syndrome”, without restrictions on dates of publication or types of study up to February 7, 2019. Germline genetic predisposition to myelodysplasia or acute myeloid leukemia is increasingly recognized in patients with seemingly sporadic myeloid malignancies; however, data are sparse to inform medical management. Reports of malignant transformation rates in Shwachman Diamond syndrome, a bone marrow failure and leukemia predisposition disorder, vary widely at 5–36%. Moreover, Shwachman Diamond syndrome is often unrecognized, particularly in older patients. A recent genomic screen of MDS patients in the CIBMTR (Lindsley et al. NEJM. 2017; 376(6): 536–47) diagnosed Shwachman Diamond Syndrome in 4% of young patients.

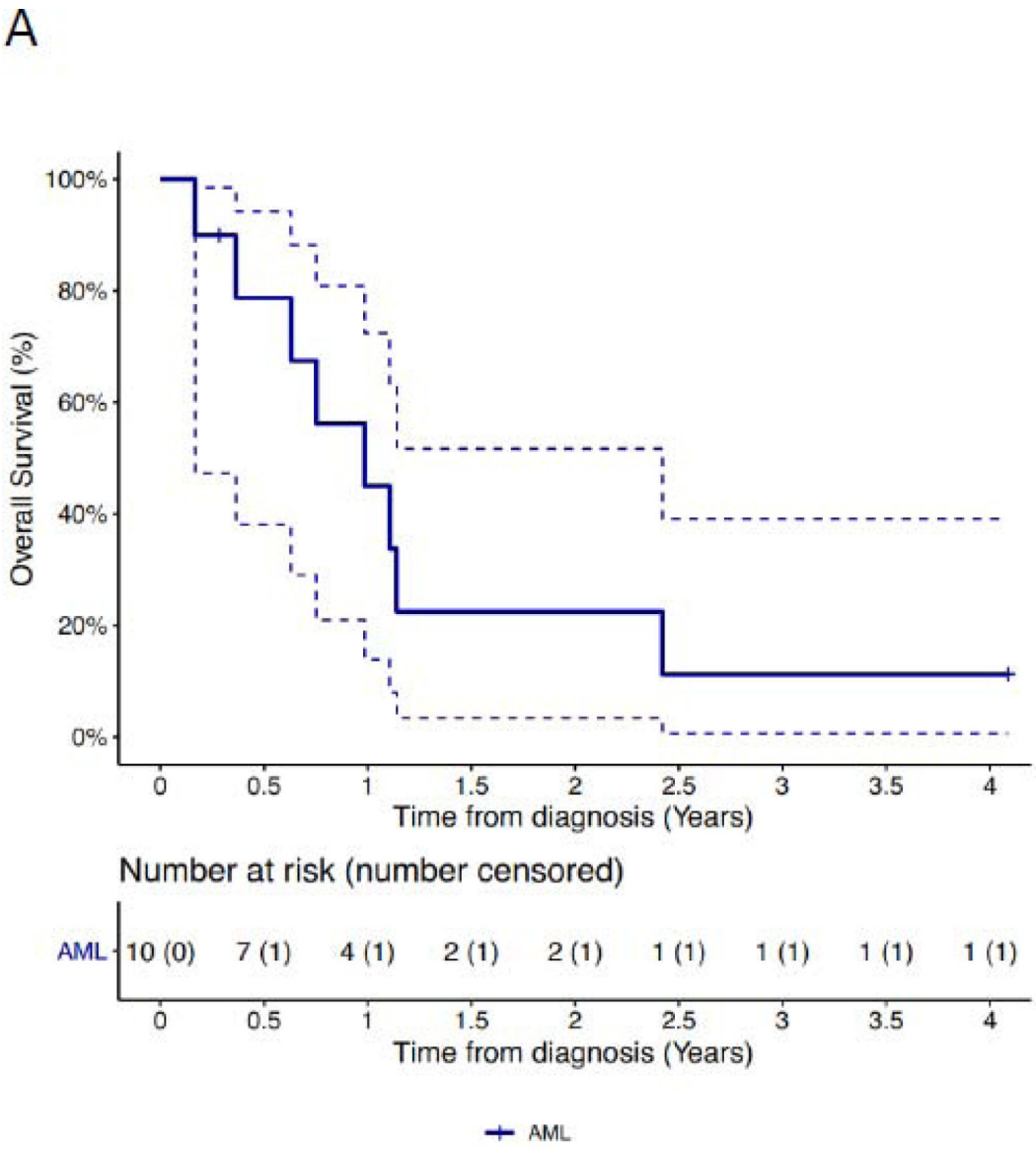
Data describing events leading up to malignant transformation in individuals with Shwachman Diamond syndrome is lacking. Baseline marrow dysmorphologies make the diagnosis of myelodysplastic syndrome challenging, and the significance of cytogenetic clones such as del(20)(q11) or isochromosome (7)(q10) and others in the absence of morphologic myelodysplastic syndrome, increasing blasts, or falling blood counts is unclear. The current expert consensus recommendation is to monitor patients for early signs of clonal evolution to facilitate early HSCT prior to the onset of acute myeloid leukemia, but data to inform frequency and method of surveillance strategies are inadequate. There is currently no consensus regarding treatment for myelodysplastic syndrome or acute myeloid leukemia in Shwachman Diamond syndrome patients, including the role of pre-HSCT cytoreductive chemotherapy or recommended conditioning regimens for HSCT.

Added value of this study

This study demonstrates that poor outcomes of acute myeloid leukemia, and myelodysplastic syndrome, in Shwachman Diamond syndrome resulted from both high treatment related mortality and high disease resistance. This study also reveals the variability and limitations of current surveillance practices, particularly potential caveats of relying on blood counts alone to detect early clonal disease. It highlights the complexities of pathologic diagnosis of malignancy in this cancer predisposition syndrome characterized by dyspoiesis, particularly in identifying advanced MDS in urgent need of expeditious transplant.

Implications of all the available evidence

The complexities of pathologic diagnosis and poor prognosis of acute myeloid leukemia and myelodysplastic syndrome in Shwachman Diamond syndrome highlight the need for expert pathologic review, and development of novel diagnostic tools for surveillance and use in prospective studies to evaluate the effect of early intervention on overall survival. Novel therapies and HSCT regimens with both decreased toxicity and improved anti-leukemic properties are urgently needed.



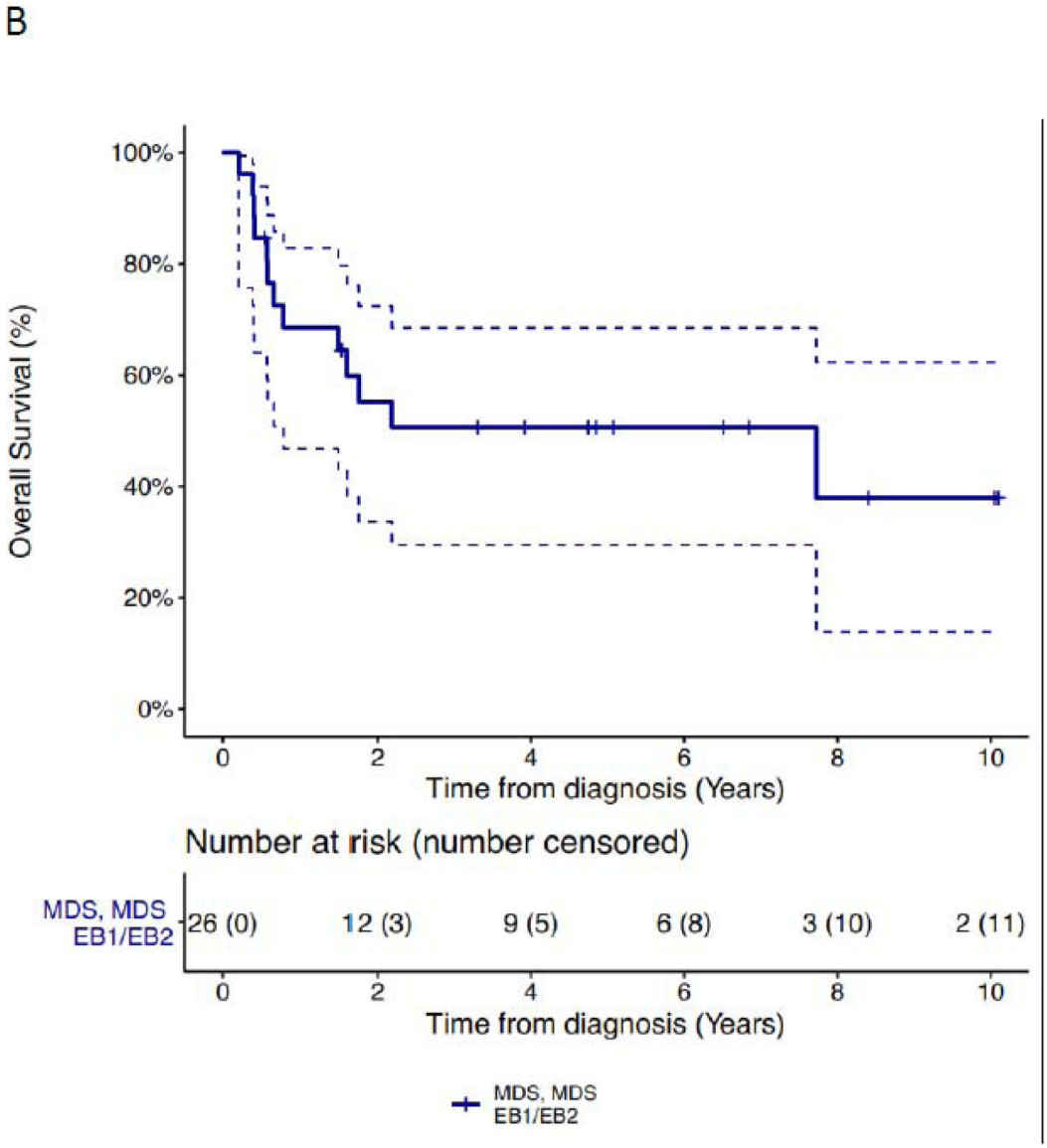
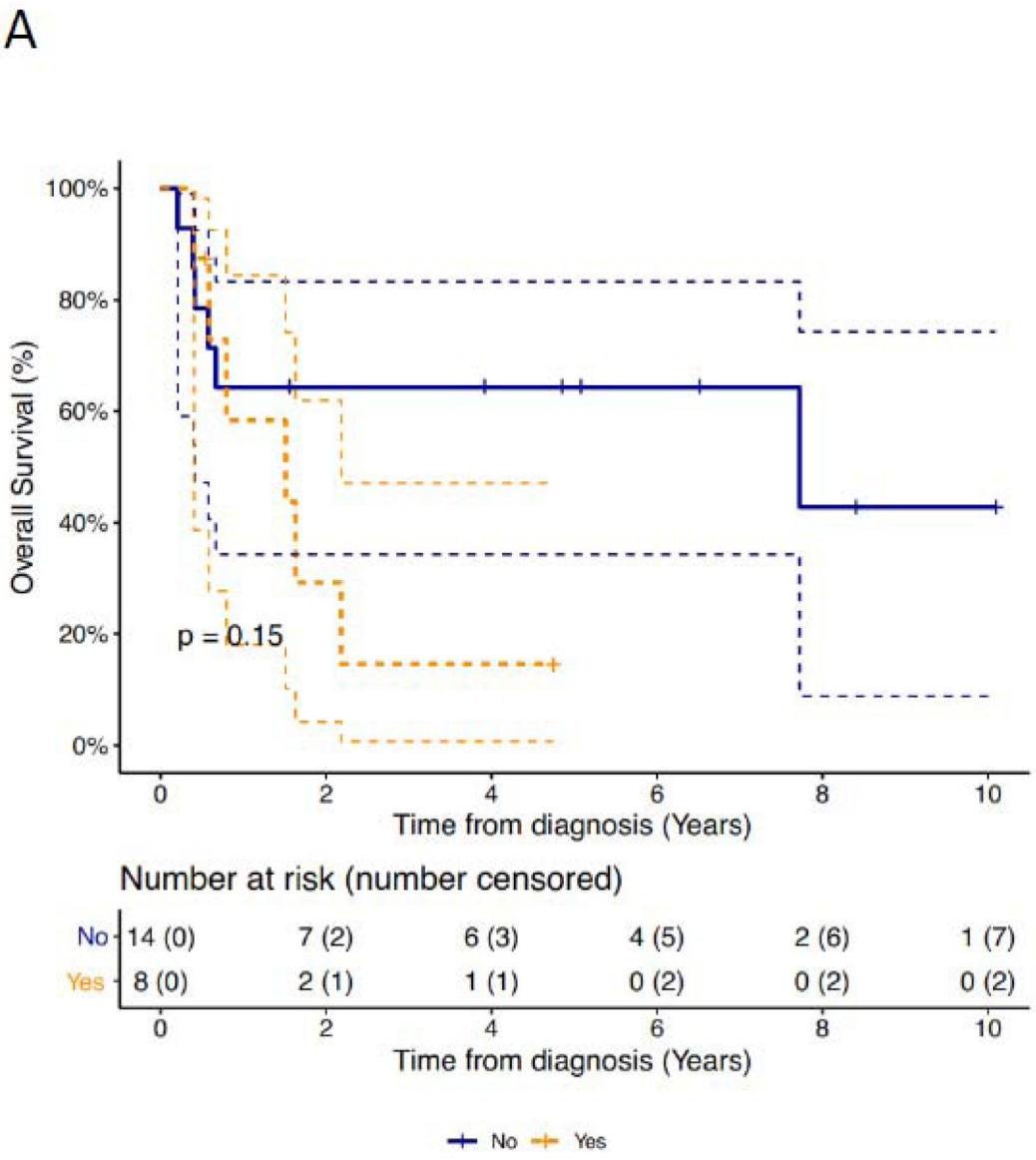


Figure 1: Overall survival of patients with Shwachman Diamond syndrome and AML and MDS.

Kaplan-Meyer curves depicting overall survival of patients with SDS and AML (A) or MDS (B) according to initial diagnosis with 95% confidence intervals (shaded areas).



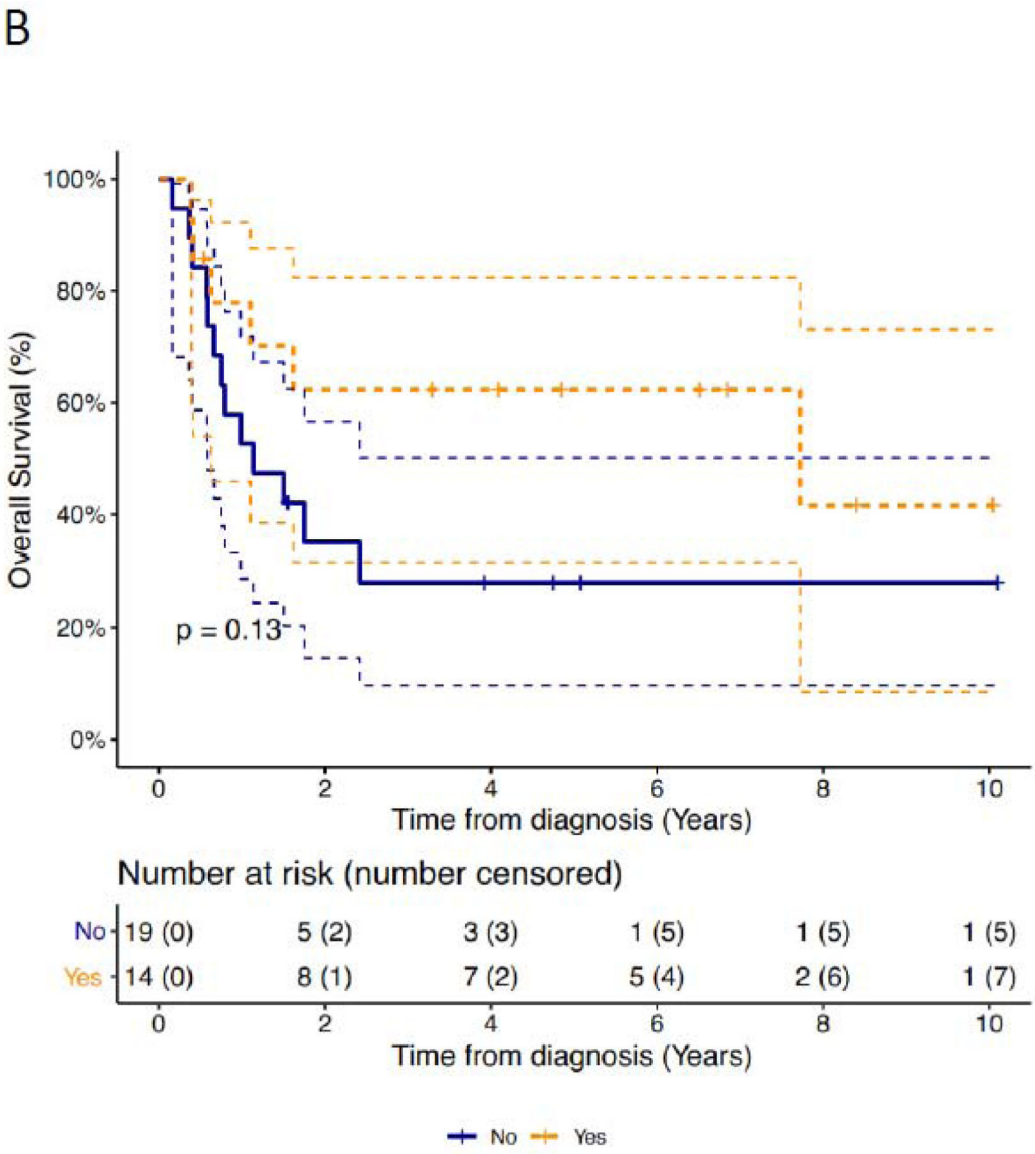


Figure 2: Overall Survival of patients with Shwachman Diamond syndrome by complex karyotype and bone marrow surveillance status.

A) Kaplan-Meyer curves depicting overall survival of patients with SDS and MDS according to complex karyotype (orange) or without a complex karytoype (blue) at initial diagnosis of MDS with 95% confidence intervals (shaded areas). B). Kaplan-Meyer curves depicting overall survival of patients with SDS and MDS or AML according to bone marrow surveillance status. Subjects who had received bone marow surveillance prior to diagnosis of MDS or AML (orange) are compared to those without surveillance prior to diagnosis (blue) with 95% confidence intervals (shaded areas).

Table 1:

Demographics and clinical features among 36 subjects

Patient-related variables	n(%)
Age at MDS/AML diagnosis	
Median (range)	18 years (0.5–47)
<18 years	17 (47)
≥18 years	19 (53)
Gender	
Male	16 (44)
Female	20 (56)
Bi-allelic SBDS mutations	
Yes	30 (83)
N/A	6 (17)
Neutropenia	
Yes	25 (69)
No	4 (11)
N/A	7 (19)
FTT or pancreatic enzyme use	
Yes	30 (83)
No	4 (11)
N/A	2 (6)
Congenital anomalies and multi-organ involvement *	
Yes	27 (75)
No	9 (14)

* denotes presence or absence of congenital anomalies or medical co-morbidities outside of the hematopoietic system

Table 2:

Diagnostic and clinical features of 36 subjects

	n (%)	Gender (male n, (%))	Median Age at MDS/AML diagnosis (range)
Local diagnosis			
MDS	18 (50)	8 (44)	14.3 (0.5–45.0)
MDS-EB1/2	8 (22)	4 (50)	16.0 (9.0–30.0)
AML	10 (28)	4 (40)	33.5 (5.5–47.0)
Central Diagnosis *			
MDS	21 (58)	11 (52)	16.0 (0.5–45.0)
MDS-EB1/2	5 (14)	2 (40)	13.8 (1.4–20.0)
AML	10 (28)	3 (30)	31.4 (5.5–47.0)
Complex Karyotype			
Yes	16 (44)	7 (44)	21.0 (9.0–47.0)
No	16 (44)	8 (50)	12.9 (1.4–45.0)
N/A	4 (11)	1 (25)	15.5 (0.5–20.0)
Bone Marrow Surveillance			
Yes	14 (39)	8 (57)	11.9 (0.5–45.0)
No	19 (53)	8 (42)	19.0 (1.4–47.0)
N/A	3 (8)	0 (0)	18.0 (19.0–37.8)

* Slides were unavailable for central diagnosis among 10/36 subjects. For these subjects the local diagnosis is used for the central review. This includes 5 AML, 4 MDS and 1 MDS-EB1/2